HAEMODYNAMIC ASPECTS OF PULMONARY OEDEMA IN VAGOTOMIZED HYPEECAPNIC DOGS

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The undersigned hereby certify that they have read and recommend to the School of Graduate Studies for acceptance, a thesis entitled Haemodynamic Aspects of Pulmonary Oedema in Vagotomized Hypercapnic Dogs submitted by Frank C. Haley, M.D., in partial fulfilment of the requirements for the degree of Master of Science.

PROFESSOR.

PROFESSOR.

PROFESSOR.

Date ..... PROFESSOR.

Respectfully dedicated to

Dr. E. A. Gain

who condoned its conception.

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INTRODUCTION

The effects on the systemic blood pressure, cardiac output, electrocardiogram, and total blood volume, of breathing high carbon dioxide mixtures, have been described by various groups of workers. No evidence of the haemodynamic changes in the pulmonary circuit following administration of carbon dioxide above the physiological range could be found in the literature. The importance of investigating fully the effects of such mixtures is emphasized by observations of Dripps, Brown and others who have measured pH in hypercapnic anaesthetized patients, and found values below seven, which they attributed to carbon dioxide retention. An additional observation of E. B. Brown, Jr. was brought to the attention of the author, and provided a stimulus to investigation of pulmonary haemodynamic changes during hypercapnia. Brown, in a note to Dr. C. Heath of this department, described his observations as follows:

> "A dog had both vagi cut in the neck and was then started on 30% CO_2. In about thirty minutes (the) tracheotomy tube was observed to be filled with froth and (the) dog's lungs were obviously filling with fluid. This had never been observed in dogs on high CO_2 before."

This work represents a continuation of the investigation into the haemodynamic effects of the high CO_2 mixtures, in particular to discover the incidence of pulmonary oedema in hypercapnic vagotomized dogs, and to measure the haemodynamic changes which occur, with a view to discovering its cause. Some of the original data from Dr. Heath's investigation into the effects of 30% CO_2 were made available, and were used as a reference for the effects of high CO_2 alone.

LITERATURE REVIEW

Effects of CO_2

Historical

Einthoven in 1892 investigated the factors influencing the bronchial muscle tone. He administered 3.7% CO_2 in air to dogs which either had an open thorax or were curarized. He found an increased resistance to inflation of the lungs but the systemic pressure was unchanged. Hundred per cent CO_2 caused a considerable increase in both resistance to inflation and arterial pressure. In dogs breathing air he cut and stimulated the vagi with marked slowing of the heart. In dogs breathing 3.7% CO_2, cutting and stimulating the vagi caused a delayed rise in arterial pressure. He made no mention of pulmonary oedema in his preparations, which were of short duration.

Itami in 1912 administered 8-10% CO_2 with 25-30% O_2 to dogs, cats and rabbits, and also to several heart-lung preparations. As anaesthetic he used ACE mixture*, urethane, or chloral hydrate. He routinely performed vagotomy. The volume changes in a limb or a segment of intestine were measured by a plethysmograph. Cardian volume and output were measured by a plethysmograph after the method of Jerusalem and Starling (1910).

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*ACE mixture consists of 1 part alcohol, 2 parts chloroform and 3 parts ether.

Itami found limb vasoconstriction during CO_2 administration even after denervation of the limb, but this vasoconstriction was abolished by high dorsal cord section. There was no vasoconstriction in limbs perfused by a heart-lung preparation when the preparation was ventilated with CO_2. In another series he found that 5% CO_2 caused an increase in blood pressure and cardiac output in intact animals, and 8-10% CO_2 also caused constriction of intestinal vessels.

These changes he attributed to CO_2 stimulation of central chemoreceptors and subsequent release of adrenalin under the influence of impulses carried in the spinal cord. He made no mention of pulmonary oedema.

Effect of CO_2 on the Circulation

The effects on the heart of increasing the CO_2 concentration in the breathing mixture supplied to open thorax preparations of dogs anaesthetized with pentobarbital-barbital were measured by Boniface and Brown (1953). They found that as the CO_2 concentrations were increased from 5 to 25% there was a proportionate decrease in the contractile force of the heart and in the amplitude of the systolic excursion. They also found a pronounced cardiac dilatation, and commented that the heart seemed to recover gradually during continued administration of CO_2 provided it was no greater than 25%. They interpreted the ECG as showing depression of the S.A. node and the conducting tissue.

Assessing the tolerance of the dog's heart to hypercapnia, Brown and Miller (1952) recorded the ECG and measured the blood pH in Pentothal anaesthetized dogs breathing 30% or higher concentration of CO_2 in O_2. They reported an initial drop in blood pressure with a rapid recovery to control or higher value. Their experiments consisted of raising the CO_2 from the original 30% until apnoea appeared, then artificial ventilation until cardiac arrest. The 30% CO_2 in O_2 was well tolerated in intact dogs, but two adrenalectomized dogs showed a profound pressure drop on 30% CO_2 with no recovery, and died when, after 2 hours, the CO_2 was increased to 40%. They quote Cavert, Johnson and Brown as having noted that a blood-perfused heart became hypodynamic as CO_2 in the oxygenator was increased beyond 30% unless adrenalin was added to the blood.

Wearn et al. (1934) observed the capillary circulation of intact cats' lungs by direct microscopic observation through a pleural window. Only a few of the capillaries in any area were seen to be "active" at any one time, and they apparently alternated between a dilated and constricted state. Ten per cent CO_2 had no discernible effect. Adrenalin usually caused an increase in the number of "active" capillaries.

Von Euler and Liljestrand, (1946) using intact cats in which a cannula had been placed in the pulmonary artery and the chest subsequently closed, found that ventilating with 6.5-20% CO_2 resulted in a rise in pulmonary artery pressure which was not

prevented by vagotomy. They concluded that there was a direct effect of the ventilating mixture on the pulmonary vasculature.

Thirty per cent CO_2 in O_2 was found to lower the pH of dogs' blood to 6.83 in 45 minutes (Spencer, 1950). Brown and Miller (1952) found a similar degree of acidosis.

While investigating the effects of breathing a 30% CO_2 in O_2 atmosphere on dogs, Billings and Brown (1955) found that after 15 minutes of hypercapnea the dogs showed an increase in haemoglobin concentration, a 20% increase in the R.B.C. count, an increased haematocrit and an increased blood volume. In dogs which had their spleen exposed and then were started on CO_2 breathing, the spleen was observed to contract, reaching its smallest size after 15 minutes. In splenectomized animals there was no significant change in the haemoglobin concentration, R.B.C. count, haematocrit or blood volume. They concluded that the dog responds to high CO_2 concentrations by contraction of the spleen. They also note that red blood cells swell sufficiently to increase their volume by 4-5% as a result of the acidosis produced by breathing 30-40% CO_2.

During initial stages of investigation of post-hypercapnic phenomena, Heath (1956) found that in the pentothal anaesthetized dog, 30% CO_2 in O_2 caused a brief initial fall in systemic artery pressure; then the pressure stabilized within 5-10 minutes, usually at a higher level than in the control period (15 of 20 dogs). One dog stabilized at the control value and the other four at lower

levels. However, of the six dogs having highest control pressures, four stabilized their pressure at a lower level while breathing 30% CO_2. His Table 7 is reproduced in part below as Table 1.

Table 1. Measured values of arterial pressure in 20 dogs breathing 30% CO_2 for two hours. (All values in mm. Hg) (Taken from Heath (1956)).

Before 30% CO_2	Min. Breathing CO_2 15-17	40-60	108-119
137	155	-	150
*170	140	-	157
*175	130	156	125
**190	205	200	200
135	155	145	130
125	140	-	138
153	170	-	155
*185	170	145	140
150	157	145	68
162	183	173	166
145	160	160	155
**175	183	180	170
125	140	121	116
*170	165	170	171
160	180	-	160
145	145	145	155
148	170	-	165
157	162	158	158
140	155	150	155
142	156	162	153
147	161	162	153

* Animals which showed a decline in systemic arterial pressure on 30% CO_2.

** Hypertensive animals which showed the usual increase in systemic pressure on 30% CO_2.

Effect of CO_2 on Isolated Perfused Lungs

Lohr in 1924 (quoted by Duke, 1949) reported that CO_2 showed a vasoconstrictor action in isolated perfused cat lungs. Duke (ibid) also quotes Binet and Bourliere (1941) as having found that CO_2 in concentrations up to 50% caused a rise in pulmonary artery pressure and an increased blood volume in isolated perfused dog lungs.

Hebb and Nimmo-Smith (1948) perfused isolated lungs of Macacus rhesus monkeys and found that ventilating with 20-30% CO_2 mixtures caused a rise in pulmonary artery pressure within 5 seconds, with no change in tidal volume. This rise was not found in eight isolated perfused dog lung experiments. However, they reported that the dog lungs showed evidence of spontaneous bronchoconstriction which they felt may have hampered ventilation.

Duke (1949) perfused isolated dog lungs with heparinized blood from the same animal. Changes in resistance were reflected by an increased pulmonary artery pressure at a constant flow, and changes in pulmonary blood volume by an altered level in the venous reservoir. When the ventilating mixture was changed from air to 5% CO_2 in air, the pulmonary arterial pressure increased and the pulmonary blood volume decreased. These changes were more pronounced when 10% CO_2 was used as a ventilating mixture.

Nissell (1950) demonstrated that while CO_2 caused vasoconstriction in the vessels of the isolated perfused cat lungs, it caused a vasodilation if the vessels had some "tone" from a previous

dose of carbaminocholine or similar parasympathomimetic agent.

Other Effects of CO_2

Hypercapnia has been shown to cause hyperkalaemia in dogs (Sealy, Young and Harris, 1954; Young, Sealy and Haris, 1954; Brown, 1955). Brown showed that 30% CO_2 in O_2 in pentothal anaesthetized dogs caused the mean plasma potassium concentration to rise gradually from control value to 4.1 mM/l to 5.9 mM/l after two hours. The mechanism and significance of this hyperkalaemia are not clear.

Low concentrations of CO_2 had been shown to provide some protection from minor stressing agents, but Langley and Kilgore (1955) showed that concentrations of CO_2 from 0-20% administered to rats produced a steady and progressive activity of the adrenal cortex, as evidenced by eosinopaenia and lowered plasma cholesteroal and ascorbic acid.

Tenney (1956) demonstrated that CO_2 is a potent stimulant to the production of sympatho-adrenal catechol amines (epinephrine and norepinephrine). He used the denervated nictitating membrane as a biological indicator in cats anaesthetized with pentobarbital and found that 15% CO_2 was a maximal stimulant. This increased production of catechol amines due to CO_2 was:

1. prevented by destroying the spinal cord
2. decreased 60% by adrenalectomy
3. unaffected by high spinal section
4. unaffected by hepatectomy.

They noted that exogenous adrenalin had little effect on cats

breathing CO_2, which they attributed to the high level of circulating endogenous adrenalin.

The problems of quantitating the amounts of adrenalin and noradrenalin in the sympatho-adrenal catechol amines was recently reviewed by von Euler (1954). He brings out the facts that the amount of noradrenalin in a tissue can be correlated with the extent of the sympathetic nerve supply, and that noradrenalin secretion in human urine is unaffected by adrenalectomy; therefore in humans the circulating noradrenalin must come from adrenergic nerves. This, presumably, would account for the decline by 60%, rather than complete abolition, of sympatho-adrenal catechol amines in adrenalectomized cats. subjected to CO_2 stress.

Evidence that 1.5-30% CO_2 is a stimulant to the adrenal cortex was listed by Richards and Stein (1957). They measured adrenal blood concentration of 17OH-ketosteroids in dogs anaesthetized with pentobarbital and breathing 21% O_2 with various concentrations of CO_2. In 10% of dogs breathing 2.5% CO_2 there was a detectable increase in 17OH-ketosteroids; in all there was a maximum increase from 20% CO_2 within 15-30 minutes. Hypophysectomy abolished the response to CO_2.

Page and Olmstead (1951) found that when dogs breathed 30% CO_2 in O_2, the femoral artery pressure declined by 40 mm. Hg and remained low. They found no change in this response after vagotomy. They used pentobarbital and curare anaesthesia. Heath (1956) using

lighter thiopentone anaesthesia observed only a transitory drop in blood pressure and an increase to above the control value.

Effects of Vagotomy

History

"The changes following bilateral cervical vagotomy have interested investigators for almost 2000 years. The procedure was apparently performed first by the Greek physician Rufus of Ephesus, who lived in the first century after Christ, and a few decades later by Galen. With the revival of science in the 16th century, interest in bilateral vagotomy was revived, and during the following centuries this procedure was performed by many experimenters, Valsalva and Morgagni being among the earlier ones. Valsalva was the first to describe pulmonary changes following bilateral vagotomy. These changes were then more thoroughly described by the French clinicians Vieusens and Senac, who called the process "inflammation". Since then the interest in this procedure has centered around the changes in the lungs."

"Summarizing the conclusions given in the literature of the 19th century, one may say there were two main schools of thought. The first considered the pulmonary lesions, i.e., pulmonary edema and pulmonary consolidation, to be secondary to various disturbances of laryngeal, esophageal, or cardiac function, while second regarded them as a primary disturbance of the function of the pulmonary vessesl." (Reichsman, 1946)

Respiration

Hoff and Breckenridge (1955) state that the vagus nerves as a source of afferent drive of the suppressor system as a part of the supramedullary regulation of respiration. They mention that vagal afferents do not influence each breath, but rather effect the tone of the suppressor system.

Farber in 1937 reported that bilateral cervical vagotomy in rabbits resulted in death from pulmonary oedema despite tracheotomy. At autopsy he reported moderate dilation of the right atrium and ventricle, engorged pulmonary vessels, and interstitial pulmonary oedema. He concluded that there might be such an entity as "neurogenic pulmonary oedema".

Tracheotomy itself was shown to cause respiratory embarrassment in rats, though rats with vagotomy survived longer with a tracheotomy than without one (Lorber, 1939). Section of the recurrent laryngeal nerves caused respiratory obstruction comparable to a complete vagotomy. Section of the vagi sparing the recurrent laryngeal nerves did not cause pulmonary oedema. Lorber blamed the pulmonary oedma following vagotomy on respiratory obstruction by mucus and the paralyzed vocal cords, leading to hypoxia and possibly cardiac failure. He thought the postulate "neuropathic pulmonary oedema" unlikely and unnecessary.

Sussman, Hemingway and Visscher (1948) gave artificial respiration by intermittent positive pressure to guinea pigs anaesthetized with Nembutal, half of which had had a vagotomy. They found that none of the animals ventilated with six mm. Hg pressure developed pulmonary oedema, while all of the animals ventilated at 20 mm. Hg pressure developed oedema. They suggested that the prolonged or high pressures of positive pressure ventilation induced cardiac failure with increased left atrial and pulmonary venous pressure leading to pulmonary oedema.

Vagotomy in open-chest cats was found by von Euler and Liljestrand (1946) to have no effect on pulmonary artery pressure.

Van Liew (1954) measured the volume changes of the chest in dogs with various inflation pressures. He found that cooling the vagi resulted in an increased lung and thorax volume with less tendency to deflation, i.e., "decreased expiratory tonus". Measurements of the intrapleural pressure indicated that the static lung tension was unaffected by vagotomy.

This was confirmed by Severinghaus and Stupfel (1955) who found an increased respiratory dead space in dogs following atropine or vagotomy.

Vagotomy was found to accelerate the production of pulmonary oedema by massive infusions of saline intravenously (Farber, 1940). Atropine did not accelerate oedema formation.

Nervous Control of Pulmonary Blood Vessels

Bradford and Dean in 1889 demonstrated changes in pulmonary artery and aortic pressures in open chest curarized dogs. They stimulated various parts of the central nervous system and found the greatest increase in pulmonary artery pressure from stimulating the thoracic spinal nerves from two to seven, or the upper part of the medulla.

According to Hoff (1955) the lungs receive both vagal and sympathetic fibres. The vagal fibres synapse in the anterior and posterior pulmonary plexuses; the sympathetic fibres, from T-1 to T-3 via the upper thoracic and inferior cervical ganglia, also pass via the pulmonary plexuses. He states that stimulation of the thoracic sympathetic or section of the vagi results in a bronchodilation. He made no mention of pulmonary vascular innervation.

In the most extensive series of dog experiments with isolated perfused lungs, Daly and co-workers (1942a, 1942b, 1948a, 1948b, 1952a, 1952b, 1954a, 1954b, 1956) concluded that there are pulmonary vasoconstrictor and vasodilator fibres (distinct from the bronchomotor fibres) which are intimately intermingled in the vago-sympathetic trunks and sympathetic nerves, and serve the pulmonary vessels of the same and opposite sides.

Evidence has been produced that the vascular bed between the pulmonary artery and the left atrium reacts to changes in left atrial pressure. Carlill and Duke (1956) perfused isolated cats' lungs with heparinized blood and found that increased left auricular pressure caused a reduction in pulmonary artery resistance. This they interpreted as due to dilation of the existing channels, the opening up of a greater proportion of the vascular channels (Wearn et al. 1934) or possibly the arterio-venous anastomotic channels demonstrated by Prinzmetal, Ornitz, Simpkin and Bergman (1948).

Bronchial artery Anastomoses

It has been noted by several workers that the bronchial arteries anastomose freely with the pulmonary vessels. Tobin (1952) traced the embryological development of the bronchial arteries in human embryos and found free anastomoses, from early embryos to viable fetuses, between the bronchial arteries, pulmonary arteries and veins, and also traced a common venous drainage by way of the pulmonary veins, bronchial veins, and the azygos vein.

Daly (1931, 1938) estimated the blood flow from the bronchial artery to the pulmonary veins in dogs as 3.5 to 41 ml. per minute. He considered (1948) the possibility that this flow was under the control of the sympathetic nervous system. The flow in the right posterior bronchial artery was measured with a bubble flow meter in 50 dogs by Bruner and Schmidt (1947). They found a peak flow of 1.25% of the cardiac output, and they considered that, even if the entire bronchial artery flow were shunted into the pulmonary venous drainage, that would not appreciably affect the pulmonary venous pressure. They found that this bronchial artery flow was controlled reflexly, with vagal stimulation causing dilation and sympathetic stimulation a vasoconstriction. High CO_2 caused an increased blood flow. Thus there does not appear to be any likelihood that increased flow from the bronchial arteries into the pulmonary system is a factor in increasing the pulmonary vascular pressures or producing pulmonary oedema.

Theory of Pulmonary Oedema

Definition

Laennec in 1834 described oedema of the lung as

> "the infiltration of serum into the substances of this organ in such degree as evidently to diminish its permeability to the air in respiration."

Visscher, Haddy and Stephens (1956) state that it is theoretically possible to distinguish pulmonary oedema at the intracellular, interstitial, and alveolar stages. The filling of the alveoli, alveolar ducts and bronchial tree with fluid and froth impairs the aeration of the alveoli and consequently reduces the functioning of the lungs. Interstitial oedema alters the lung elasticity and may affect the extravascular pressure on the lung vessels. Intracellular oedema is of minor importance.

History

The oldest theory of pulmonary oedema based on physiological grounds is that advanced by Cohnheim and Lichtheim in 1877 and Welch in 1878. Their theory postulated a decreased output from the left ventricle, an increased pulmonary vein pressure, and transudation of fluid into the lung, i.e., pulmonary oedema. Welch is quoted by Visscher et al. (1956) as having stated that the major mechanism in acute pulmonary oedema is,

> "a disproportion between the working power of the left ventricle and the right ventricle of such character that, the resistance remaining the same, the left side of the heart is unable to expell in a unit of time the same quantity of blood as the right heart"

and,

> "It is hardly necessary to state that such factors as changes in osmotic pressure, alterations in the capillary endothelium and interference with the absorption of lymph, which have become prominent in the later discussion of the cause of oedema, may be utilized in the explanations of pulmonary oedema as of congestive oedema elsewhere, but I find great difficulty in conceiving any of these factors alone to be the primary cause of acute general oedema of the lungs."

Sahli in 1885 recorded that obstruction of the pulmonary venous drainage by constriction of the left atrium resulted in pulmonary oedema.

Modrakowsky demonstrated (1914) that isolated lung lobes could withstand high arterial perfusion pressures without apparent harm provided that venous outflow was unobstructed. Impairment of venous drainage, with even moderate elevation of the perfusion pressure, resulted in pulmonary oedema.

Isolated lung lobes were used in a biological oxygenator for total bypass experiments by Campbell, Crisp and Brown (1955). To minimize pulmonary oedema in the lung lobes, they found it necessary (1) to ensure complete patency of the pulmonary veins, (i.e., no pulmonary vein "back pressure"); (2) to place a depulsator between perfusion pump and pulmonary artery to protect the pulmonary artery from very high pressure impulses; and (3) to ventilate the lung lobes with inflation pressures not exceeding 16 cm. of water. Neglect of these precautions resulted in oedema and congestion of the isolated lung lobes.

"Neurogenic" Pulmonary Oedema

Many investigators in the past have sought to explain the pulmonary oedema which developed as a terminal event in patients and experimental animals on the basis of some neurological lesion without specifying the exact nature of this lesion. Thus the pulmonary oedema found in guinea pigs following vagotomy, even with tracheotomy (Farber, 1937), patients with head injury (Moutier, 1918) and in patients with neurological lesions (Cameron and De, 1948) have all been ascribed to a possible neurogenic factor. This has been sometimes taken to mean the total disturbance, i.e., the slow pulse, decreased cardiac output, increased venous pressure and subsequent pulmonary oedema, following increased intracranial pressure (Campbell, Haddy, Adams and Visscher, 1949) or the tachycardia, increased systemic and left atrial pressures, and pulmonary oedema following intracisternal fibrin (Cameron and De, 1949; Sarnoff and Sarnoff, 1952). At other times the term "neurogenic" has been used to mean a postulated increased capillary permeability following loss of nervous control (Farber, 1937; Engel, 1941).

Gamble and Patton (1951, 1953) used the term to explain the pulmonary oedema which develops in rats with preoptic lesions to the hypothalamus. They postulated an "oedemagenic centre" in the posterior hypothalamus. Later work by Maire and Patton (1956) showed that this oedema was the result of haemodynamic changes

following massive sympatho-adrenal activity. Splanchnic nerve section reduced the incidence of pulmonary oedema following preoptic lesions; cervical cord section prevented it, but vagotomy was of no benefit. Injection of the adrenalin of the animal's excised adrenals or the equivalent amount of commercial adrenalin caused a response identical to that from the preoptic lesion. However, adrenal demedullation did not protect the animal with a preoptic lesion.

The explanation proposed for the development of pulmonary oedema under these circumstances was a massive release of adrenalin which was accompanied by a generalized splanchnic vasoconstriction. Both these factors caused a sudden shift of blood from the greater to the lesser circulation, with the development of oedema following from this sudden overloading of the pulmonary vasculature.

A similar explanation had been offered for the pulmonary oedema following intravenous ammonium ions (Koenig and Koenig, 1949; MacKay, Jordan and MacKay, 1950), hypoglycaemia (MacKay and Pecka, 1950), inspiratory and expiratory resistance (Zinberg, Nudell, Kubicek and Visscher, 1948), intracisternal fibrin (Cameron and De, 1949). Cameron and De (1949) described the response of rats to intracranial fibrin as a tonic contraction of voluntary muscles, piloerection, bulging of the eyeballs, dilation of pupils, and occasionally passage of urine and faeces. Rats took a deep inspiration and then rapid gasps. Rabbits took one or two

deep breaths. and then were apnoeic. At autopsy they found the lungs filling the chest without collapsing when the pleura was opened. There were dark red congested patches on the lung, the pulmonary vessels were distended, and commonly the right side of the heart was dilated. On microscopic section the lung blood and the lymph spaces were tremendously dilated, particularly the latter. This, they stated, is the picture produced by large intravenous injection of adrenalin.

Sarnoff and Sarnoff (1952) confirmed these observations, finding an elevation of systemic arterial and left atrial pressures following intracisternal fibrin. Vagotomy gave no protection. but on the contrary caused a further rise in left atrial pressure and more rapid development of pulmonary oedema.

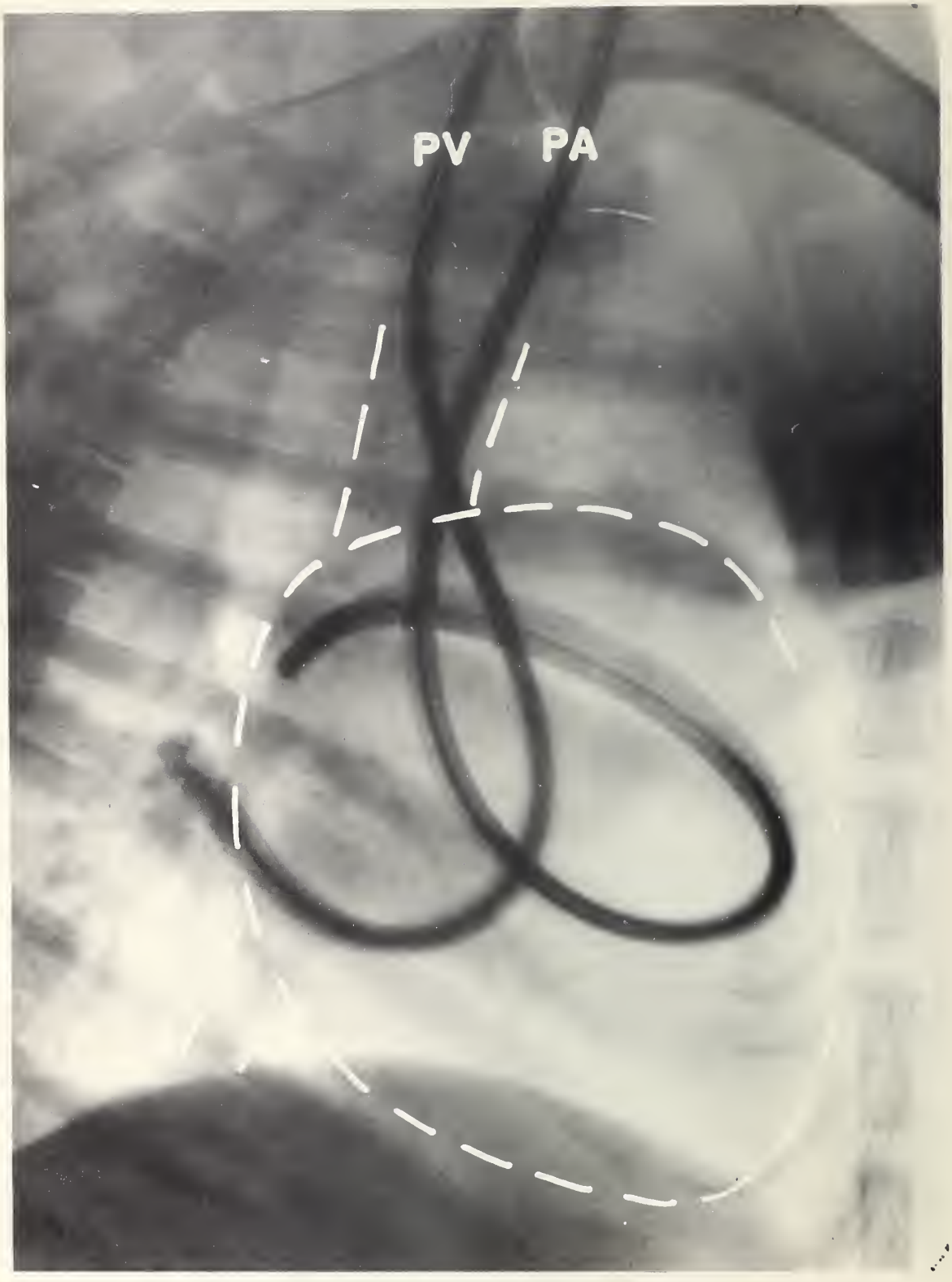
Procedures which have been found to protect animals from these oedemagenic insults include spinal anaesthesia, Arfonad and phlebotomy (Sarnoff and Berglund, 1952), adrenolytic drugs SKF 501 and SY-2 (MacKay, Jordan and MacKay, 1950), Dibenamine, adrenalectomy, cold and subcutaneous formalin (Koenig and Koenig, 1949), total sympathectomy (Sarnoff and Sarnoff, 1952), adrenalectomy or adrenal demedullation (MacKay and Pecka, 1950). They share the common property of decreasing the shift of blood from the peripheral and splanchnic areas into the lesser circulation by preventing the stimulation of the adrenals, the vasoconstriction following its release, or decreasing the quantity of blood in the vascular bed.

The pulmonary oedema which follows an increase in intracranial pressure has a different cause. The heart rate is slowed, the cardiac output decreased and the pulmonary venous pressure elevated. Vagotomy or atropine prevent this heart failure situation, and pulmonary oedema does not develop where these have been used.

Lymph Drainage of the Lungs

Two groups of workers (Drinker, 1947; Paine et al., 1949) measured lymph flow from the lungs. Drinker was able to cannulate the right thoracic duct and to prove, in about half the cases, that it carried carried all of, and only, lymph from the lungs. In cases where this could be shown, he measured the lymph flow during the development of pulmonary oedema, and found that there was a greatly increased flow preceding and during pulmonary oedema. These findings were confirmed by Paine et al., (1949). They found that the lymphatic system could carry a greatly increased load without embarrassment. Qualls, Curtis and Menelly demonstrated that a dog could absorb relatively large amounts of intra-tracheal fluids (normal saline or distilled water).

Heemstra (1956) mentions that respiratory movements particularly excursion of the diaphragm are of paramount importance for lung lymph drainage.



INTRACARDIAC CATHETER

Fig. 1

Figure 1.

Radiograph of a dog with pulmonary artery and pulmonary vein catheters in position. The pulmonary artery catheter has been passed through the right jugular vein, superior vena cava, right atrium and ventricle, and the tip lodged just into the outflow tract. The pulmonary vein catheter has been passed retrograde through the left carotid artery, aorta, left ventricle and atrium, and the tip positioned just beyond the heart shadow. The approximate size of the heart shadow has been shown by dashed lines. Because of the relatively long exposure time, the outline of the beating heart is blurred in the radiograph.

EXPERIMENTAL METHOD

Induction and Incision

Mongrel dogs weighing eight to 15 kilograms were anaesthetized with sodium thiopentone (thiopentobarbital, "Pentothal") 25 to 33 mgm. per kilogram intravenously as a 5% solution in normal saline. The neck and femoral areas were clipped, and the dog fastened supine to a dog board. Through a midline incision the trachea was exposed and a large transparent plastic cannula was tied into a tracheotomy. Both carotid sheaths were exposed and loose ligatures placed about the vagi and carotid arteries. Through a separate incision the right jugular vein was exposed and ligated at the cephalad end of the incision.

Cardiac Catheters

Under direct fluoroscopy, in the left lateral position, a siliconed radio-opaque 8F Cournand catheter was passed through the right jugular vein, right atrium and ventricle, and the tip advanced until it lay in the pulmonary artery at the edge of the heart shadow. The approximate pressure was measured by a water manometer, and patency proven by withdrawing blood. A second 8F catheter was passed retrograde through the left carotid artery, aorta, left ventricle, and into the left atrium. Pressure and patency were checked, a slow drip of heparinized saline (1:50,000)

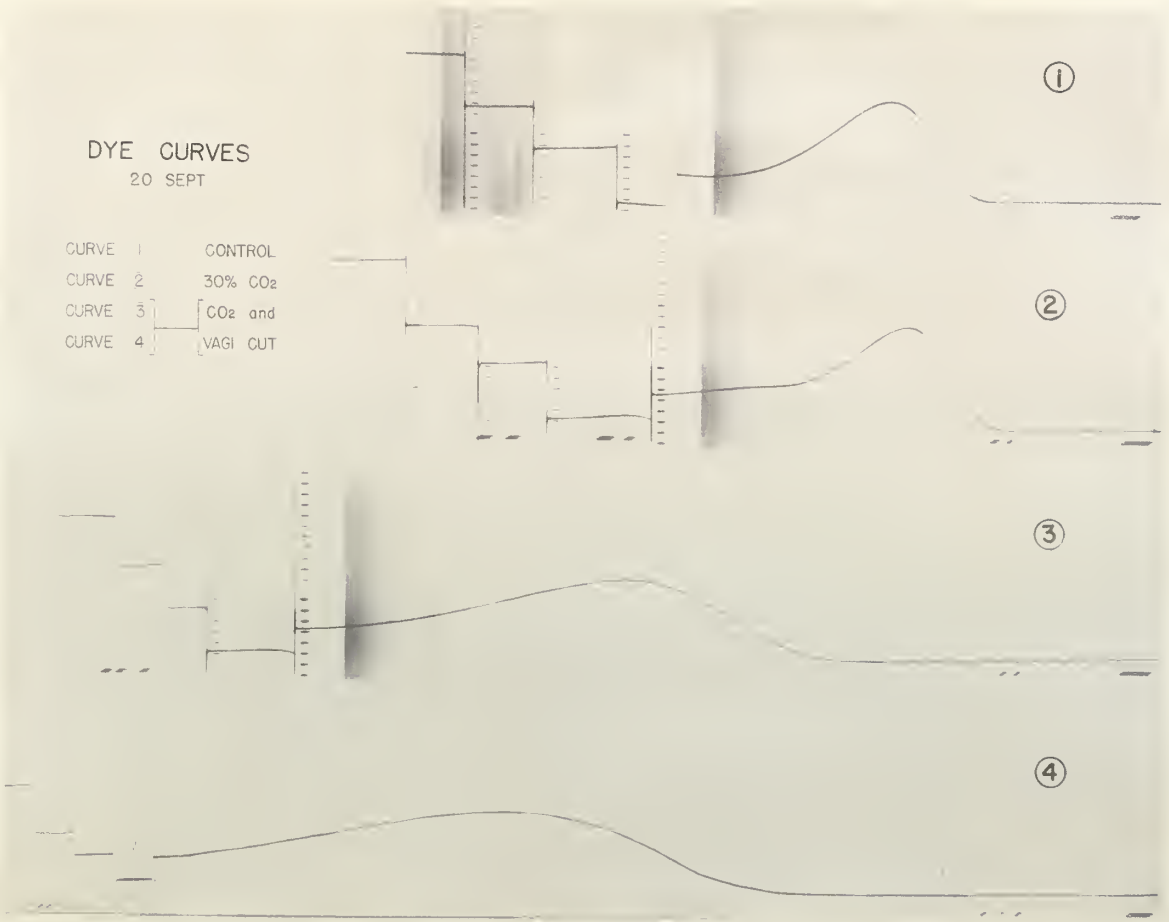

DYE CURVES
20 SEPT
CURVE 1 CONTROL
CURVE 2 30% CO2
CURVE 3 CO2 and
CURVE 4 VAGI CUT
①
②
③
④

Fig. 2

Figure 2.

Dye curves for cardiac output estimation. Dye injection is indicated by signal mark at the bottom right of each curve. One second vertical time lines, which may be seen faintly in this photograph are clearly defined on the original record.

The straight base lines are characteristic of dye curves recorded using the present equipment. Galvanometer deflections at the left are due to known concentrations of dye in blood drawn immediately before the curve was recorded. Calibration curves were constructed from these latter tracings.

Curve (1) was recorded from the anaesthetized dog breathing air; curve (2) - 15 minutes after beginning CO_2 breathing; curve (3) - 15 minutes after vagotomy; and curve (4) - 55 minutes after vagotomy.

The protocol of this experiment appears on page 29. No significant change occurred between (1) and (2). Curves (3) and (4) show a marked decline in output and a slight increase in central blood volume. See Table 3a on page 36.

was started through the catheters to prevent clotting. A radiograph of the catheters in position is shown in Fig. 1 (cf. Rahn, Stroud and Meier, 1952).

Pressure Recordings

On return to the lab plastic polythene catheters were installed in both femoral arteries, the one in the right femoral 1.9 mm. O.D. and that in the left 3.8 mm. O.D. This latter was tied into position with the tip at about the level of the diaphragm, and was connected to a Wood oximeter cuvette (model XC-50B). The smaller catheter was connected to a Statham PR23-5D-300 pressure transducer. Both intracardiac catheters were connected through three-way stopcocks to a Statham model P23B pressure transducer, pulmonary artery and pulmonary vein pressures being read alternately. Both transducers recorded on a Sanborn Twin-Viso (model 60-1300) direct writing oscillograph and were calibrated against a mercury manometer. Calibration and zero drift were checked during the experiment. Mean pressures were obtained by a "meaning" circuit in the strain gauge amplifier. Samples of original recordings are shown in Fig. 2.

Cardiac Output Measurement

Cardiac output was measured using a modification of the dye dilution method of Hamilton (Dow, 1956). After

heparinization a 20 ml. sample of blood was drawn from the left femoral artery and accurately measured into five ml. volumetric flasks. Graded amounts of Evans blue dye (T-1824) were added from a Burroughs-Wellcome micrometer syringe.

A fixed amount of the same batch of dye was delivered from a Chaney (1938) type syringe into the pulmonary artery through the siliconed catheter. The time of injection was automatically recorded by a marker light controlled by a pressure actuated switch fastened to the plunger of the injection syringe. Blood from the aorta was sampled by drawing blood through the left femoral artery catheter and the cuvette at a constant rate of 25 ml. per minute into a motor-driven 21 ml. syringe. Sampling continued for 15-30 seconds, requiring 6-12 ml. of blood. The blood was returned to the animal. The 5 ml. dyed blood samples previously obtained were then drawn through the cuvette using the same technique.

The output of the photocell of the cuvette was led through an Ayrton shunt to an electrically damped galvanometer (G.E. model 9892909G14). Galvanometer deflection was recorded on a six inch photokymograph with a paper speed of 1.4 cm. per second. Deflections due to dye in the blood were measured against the deflections produced by the known amounts of dye in the five ml. calibration samples. This blood was returned to the animal. Discharges of a gas-tube at one second intervals gave time

calibrations. Sample curves are shown in Fig. 3 with the calibration deflections after each curve. Note that curves read from right to left. Four to eight curves were recorded from each animal.

Carbon dioxide and oxygen were mixed in a six litre bag and administered through the tracheotomy tube and an open system. The CO_2 concentration was measured at intervals using a Scholander (1942) type analyzer.

Calculations

Mean systemic arterial, pulmonary arterial and venous pressures were read from the oscillograph record and plotted on graph paper.

Cardiac output and "central blood volume" were calculated using the method of Dow (1955, 1956). Central blood volume was calculated from the cardiac output and the mean transit time. This volume includes the pulmonary blood vessels beyond the tip of the pulmonary artery catheter, the left atrium and ventricle, the aorta to the tip of the campling catheter, and all "temporally equivalent vessels".

In one dog the dye was injected into the pulmonary vein (instead of the pulmonary artery). Assuming complete mixing, this permitted an estimate of the central blood volume excluding the pulmonary bed.

In a number of experiments in which oedema was observed, the curves recorded after the oedema developed were so prolonged and flat that it was not possible to extrapolate the curve in the conventional manner. Dow (1955) who described curves of this type, derived an "Emergency Formula" which was tried, testing it against the values obtained from the conventional method when this was possible. Correlation was poor and since it was considered that the method could not be used with confidence the results of experiments of the above-mentioned type were discarded.

The cardiac index was calculated from the cardiac output divided by the surface area in square meters. (from Meehs formula using Rubners constant, surface area = 112 x weight in grams $^{2/3}$).

Central blood volume was calculated as litres per kilogram of body weight.

Evaluation of Pulmonary Oedema

In a preliminary series of 12 rabbits the ratio of lung weight after excision to the weight after drying was used as an index of pulmonary oedema. The mean wet-dry ratio in the lungs which had gross oedema was 6.74 with a range of 6.13 to 7.40; in the lungs which did not show gross oedema, the mean was 5.33, with a range of 4.91 to 5.75. This showed complete correlation

of gross examination with the wet-dry method of evaluating pulmonary oedema.

In the dog series when pulmonary oedema developed, usually within half an hour of the hypercapnia and vagotomy, rales were readily audible, and usually froth appeared in the transparent tracheotomy tube. Sometimes froth and oedema fluid filled the respiratory gas system, flooded the valves and ran onto the floor. Gross oedema was so unmistakeable when present, and had coincided so exactly with the wet-dry ratios in the rabbit series, that it was used as the criterion of pulmonary oedema. The validity of this approach was confirmed by Visscher, Haddy and Stephens (1956).

Statistical Method

In the examination of the significance of the differences in pressures between groups, the Standard Deviation was found from the formula:

$$S_x = \sqrt{\frac{\sum x^2}{N} - \bar{x}^2}$$

where x is the variable measured

$\sum x^2$ is the sum of the squares of x

S_x is the standard deviation

N is the number of measurements of x

$\bar{x}^2$ is the square of the mean value of x

and the Standard Error of the Mean from:

$$SE\ \bar{x} = \frac{S_x}{\sqrt{N-1}}$$

The significance of the variance, σ, was found from:

$$\sigma_{\bar{x}_1 - \bar{x}_2} = \sqrt{\frac{N_1 S_1^2 + N_2 S_2^2}{N_1 + N_2 - 2}} \times \frac{N_1 + N_2}{N_1 \times N_2}$$

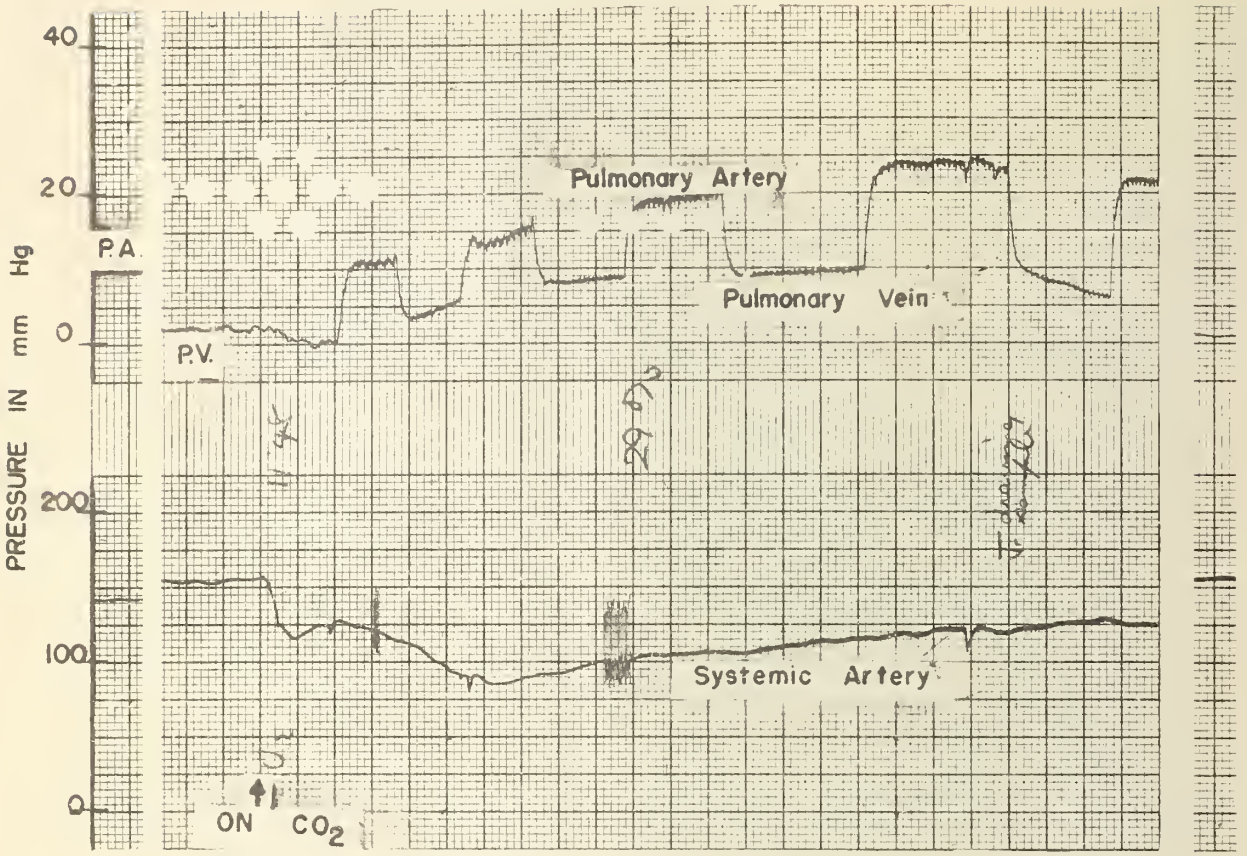
and t (Fisher "t test") from

$$t = \frac{\bar{x}_1 - \bar{x}_2}{\sigma_{\bar{x}_1 - \bar{x}_2}}$$

with $N_1 + N_2 - 2$ degrees of freedom

P values were found from the double tail table in Treloar (1951).

Effect of Hypercapnia on Systemic
& Pulmonary Blood Pressure



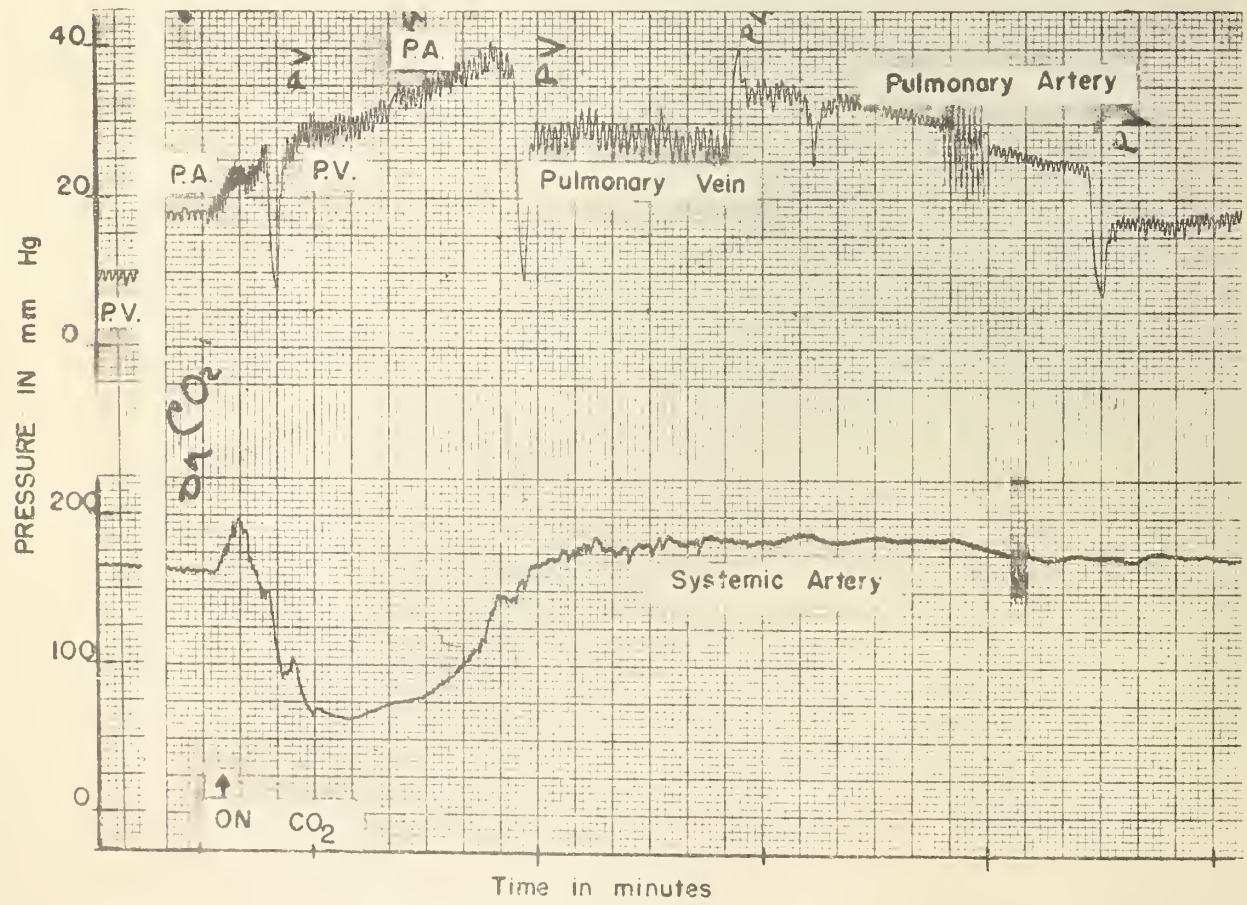


Fig 3a Portions of actual records

Figure 3a.

Effects of hypercapnia on systemic and pulmonary blood pressure.

These records are from two experiments, in each case the upper record alternates between pulmonary artery and pulmonary vein pressures, the lower record is systemic artery pressure. These are mean pressures apart from short bursts of pulsatile pressures. Time scale for both tracings are shown at the bottom, pressure calibration is shown at the left.

The usual rise in pulmonary artery and pulmonary vein pressures is best seen in the top tracing. The typical drop in systemic artery pressure and subsequent rise to control value or higher is also shown.

Effect of Vagotomy on Systemic

& Pulmonary Blood Pressure

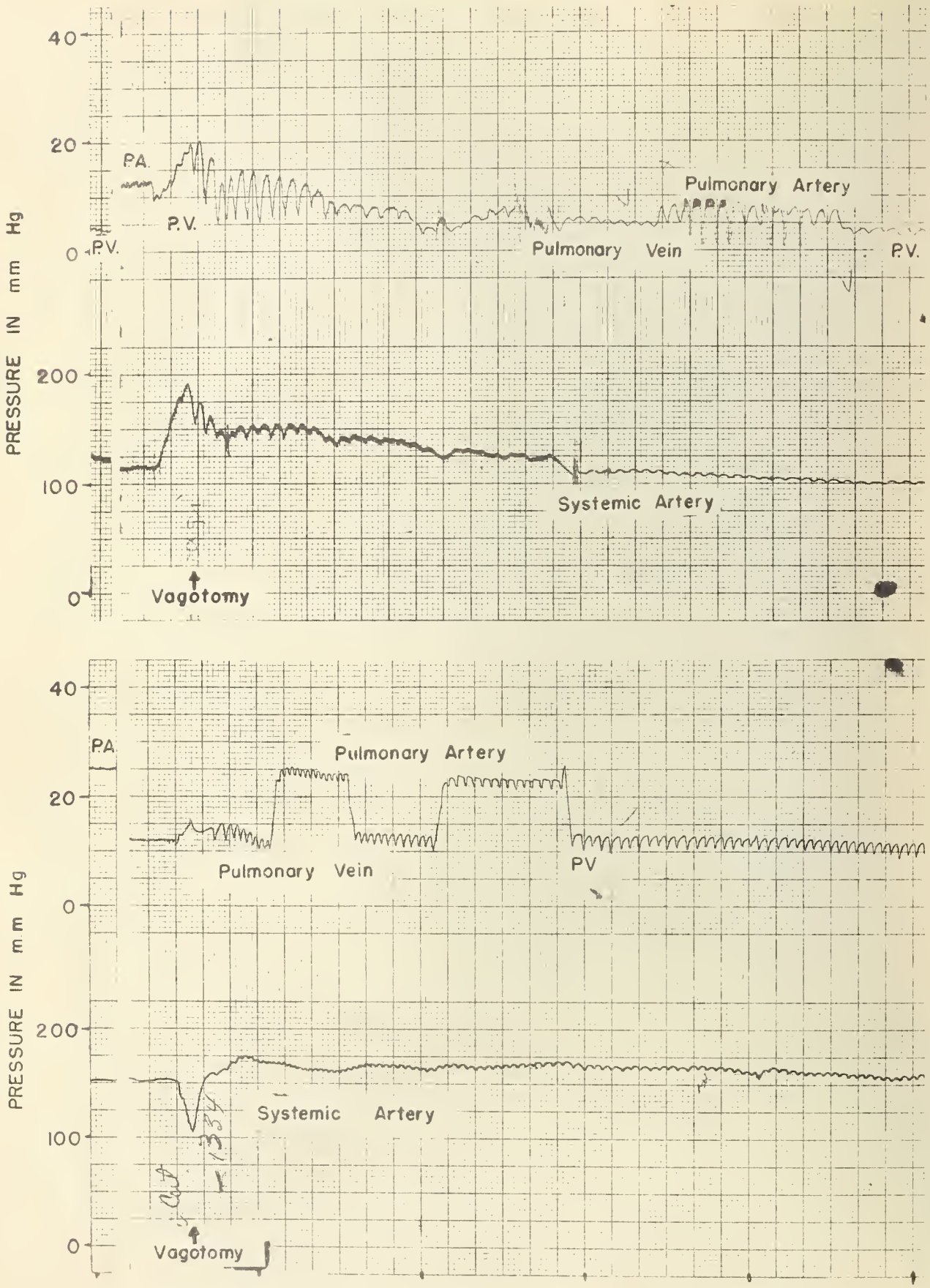


Fig. 3b

Portions of actual records

Figure 3b.

Effect of vagotomy on systemic and pulmonary blood pressure.

A transient rise in pulmonary pressures followed by a progressive decline is shown. The brief drop in systemic pressure shown in the lower tracing frequently occurred during handling and cutting of the vagi. Following vagal section, there was an increased systemic pressure which gradually fell.

Waves in the mean pulmonary pressures are due to respiratory movements which are more pronounced after vagotomy. See also Fig. 3c.

Effect of Vagotomy & Hypercapnia
on Systemic & Pulmonary Blood Pressure

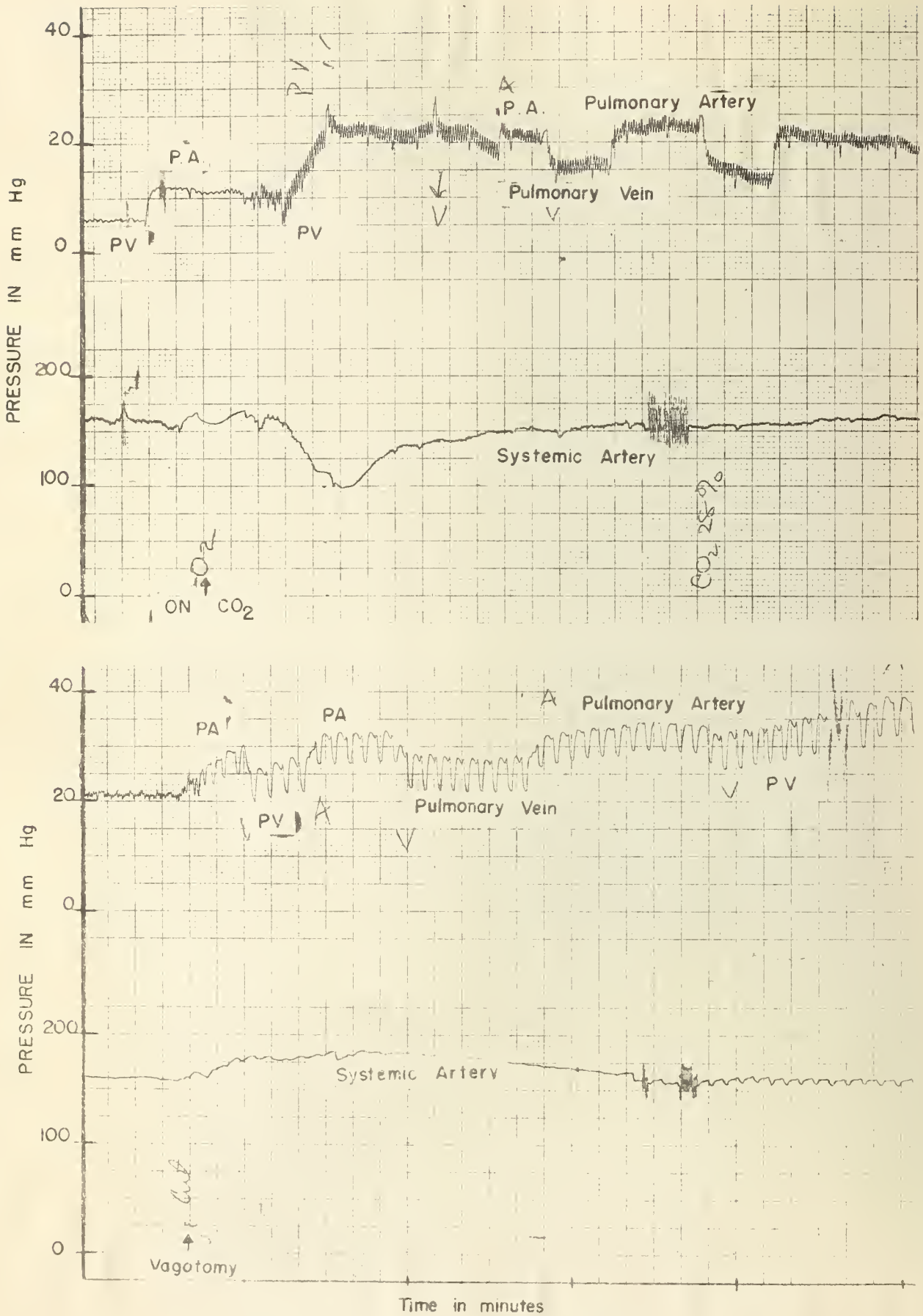


Fig 3c Portions of actual records

Figure 3c.

Effect of vagotomy and hypercapnia on systemic and pulmonary blood pressure.

These records are from the same dog and were made on 20 September. The upper trace shows the usual changes when CO_2 is administered, the lower tracings show that in hypercapnic dogs vagotomy produces elevation of all pressures without the subsequent fall seen in Fig. 3b. Pulmonary pressures continue to rise throughout the five minute trace. (Protocol of this experiment is shown on page 29, output dye curves are shown in Fig. 3, page 23, and the cardiac output and central blood volume are in Table 5a, page 36.)

RESULTS

A total of 43 dogs was used in this study. The records of five dogs were discarded because of mediastinal emphysema (one dog), cardiac arrest (two dogs) or respiratory arest after vagotomy (two dogs). One dog developed severe pulmonary oedema after the cardiac catheters had been passed but before pressures could be recorded. Cardiac arrest occurred in one dog, and respiratory obstruction killed another. Thus eight dogs produced no useful records.

Pressure recordings were obtained from 22 dogs which breathed 30% CO_2 and had bilateral vagotomy. Of these 13 developed pulmonary oedema. However, three experiments were discarded because pressures recorded from the pulmonary artery and vein catheters were so similar. It was felt that these represented cases in which one of the catheters had become "wedged" and was recording so-called "wedge" pressure (see Mueller, Gensinin, Previdel and Blount, 1954; Shafer and Silber, 1956; Connally, Kirklin and Wood, 1954). At times the "venous" catheter pressure exceeded the "arterial". In later experiments where this was observed, manipulation of the catheter tip or withdrawing it slightly corrected the anomalous readings.

Nine dogs breathed 30% CO_2 in O_2 and had a bilateral cervical vagotomy but did not develop pulmonary oedema.

Seven dogs had vagotomy only. None developed pulmonary oedema during the experiment, but one had some reddish froth in the trachea at autopsy. This froth was felt to have been due to pulmonary haemorrhage. Complete pressure refordings are available for six of these dogs.

Three dogs were hypercapnic without vagotomy. They were in every way comparable with the dogs investigated by Heath and Brown (1956) whose work was used as control for the effects of 30% CO_2 in O_2 on Pentothal anaesthetized dogs. See Table 1, page 6.

Four dogs breathed 30% CO_2 in O_2, had a cervical vagotomy, and also received a sympatholytic drug, Arfonad, Dibenamine or Regitine. One died immediately after the drug was given; none showed evidence of pulmonary oedema.

Protocol of typical experiment, Sept. 20, 1956.

14.4 kilogram dog
09:35 Anaesthetized with Pentothal 7 ml. intravenously.
09:55 Pulmonary vein and artery catheters passed under direct fluoroscopy. Slow drip heparinized saline started.
10:27 Catheters installed in left and right femoral arteries.
11:10 Pentothal 1 ml. i.v.
11:50 Pentothal 2 ml. i.v.
12:15 Heparin 2 ml. i.v.
12:25 Dye curve No. 1.
12:35 Started on 30% CO_2 in O_2.
12:50 Dye curve No. 2.
12:55 Good breath sounds.
12:56 Vagotomy, bilateral cervical.
13:11 Dye curve No. 3.
13:19 ?? Rales in chest.
13:22 Heparin 1 ml. i.v.
13:33 Chest clear.
13:49 Heparin 1 ml. i.v. Generalized coarse bubbling rales in chest.

MEAN PRESSURE CHANGES IN DOGS FOLLOWING 30% CO_2 AND VAGOTOMY

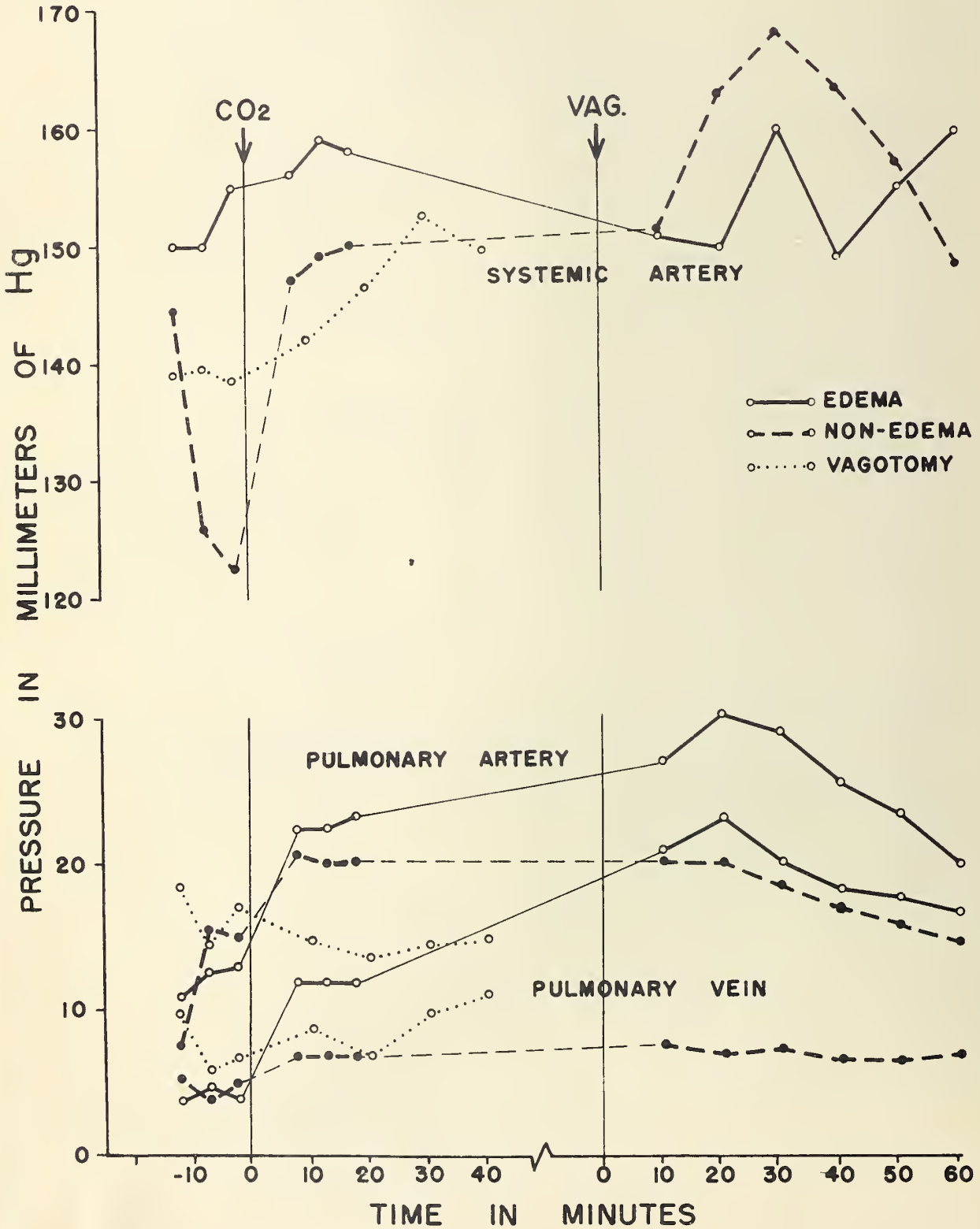


Figure 4.

This figure shows the systemic, pulmonary artery and pulmonary vein pressures. To the left of the first vertical line is the control period. At the line "CO_2" the dogs were given 30% CO_2 in O_2 and the pressure changes are indicated. After a variable period, during which the pressures stabilized, the vagi were cut. This is indicated by the second vertical line "Vag". The interval between CO_2 and vagotomy was approximately 30 minutes (Pressures after vagotomy are shown to the right of the "Vag." line. The dogs which had vagotomy only, are shown in the control period and immediately to the right of the "CO_2" line, to permit comparison of the effects of hypercapnia alone with the effects of vagotomy alone.

13:51 Dye curve No. 4.
14:05 Froth in tracheotomy tube.
14:19 Killed with overdose of Pentothal.

At post mortem, lungs pillowy and crepitant, exude froth on sectioning. Catheters found in good position. Final diagnosis -- pulmonary oedema.

Mean systemic arterial, pulmonary arterial and pulmonary venous pressures after the preparations were complete, before hypercapnia or vagotomy, and the mean pressures after both procedures had been completed, are shown in Table 4 and Fig. 4. Also shown are pressures for dogs having vagotomy only and dogs hypercapnia only.

In presenting experimental results the experiments are categorized as follows:

1. Oedema dogs (13 dogs) - hypercapnic, bilaterally vagotomized dogs which developed gross pulmonary oedema.
2. Non-oedema dogs (9 dogs) - hypercapnic bilaterally vagotomized dogs in which oedema did not develop.
3. Vagotomized dogs (7 dogs) - bilaterally vagotomized dogs.
4. Hypercapnic dogs (3 dogs) - dogs breathing 30% CO_2 in O_2.
5. Sympatholytic dogs - hypercapnic bilaterally vagotomized given infusions of sympatholytic drug.

RESULTS

Effects of CO_2 and Vagotomy on Blood Pressure

Thirty per cent CO_2 caused a slight increase in systemic pressure in the oedema dogs. In the non-oedema dogs there was a greater

rise, but not to the level of the oedema dogs, whose initial pressure had been greater. High CO_2 caused an increase in the pulmonary artery and vein pressures of oedema dogs, which was much more marked than in the non-oedema dogs.

Vagotomy in the oedema dogs caused a slight decrease in systemic pressure, while in the non-oedema dogs there was a further rise. Pulmonary artery and vein pressures rose sharply in the oedema dogs, moderately in the non-oedema dogs, and not at all in the dogs breathing air.

It is noteworthy that the pulmonary vein pressure in the oedema group was higher than the pulmonary arterial pressure in the non-oedema and vagotomy groups.

Table 2 shows the effects on systemic, pulmonary artery and pulmonary vein pressures of the 30% CO_2 mixture. Mean pressures are shown for three 5-minute periods before hypercapnia, and for three 5-minute intervals immediately afterward, omitting one 5-minute period during which the air was flushed from the respiratory tubing.

Table 2. Effects of CO_2 on systemic and pulmonary blood pressure.

	Time in minutes after starting CO_2					
	-15 -10	-10 -5	-5 0	5 10	10 15	15 20
Systemic artery						
oedema	151	152	156	156	159	158
non-oedema	130	127	126	147	149	150
Pulmonary artery						
oedema	12	12	10	23	23	24
non-oedema	15	15	15	21	20	20
Pulmonary vein						
oedema	4	3	4	12	12	12
non-oedema	5	5	5	7	7	7

Effects of CO_2 on Respiration

When 30% CO_2 was administered, the rate and depth of respiration increased so that it was necessary to increase the gas flow from about 5-8 litres/min. of O_2, which kept the mixing bag inflated, to about 20 or even 30 litres/min. when 30% CO_2 was added.

Vagotomy caused a slowing of respiration. In dogs breathing air, the mean respiratory rate was 54 per minute; following vagotomy the mean rate was 18 per minute. See Table 3 below.

Table 3. Respiratory rate before and after vagotomy.

	Respiratory Rate		Ratio
	Before	After	After/before
	32	27	0.84
	64	27	0.42
	35	13	0.37
	22	9	0.41
	38	19	0.50
	90	13	0.14
	100	15	0.15
Mean	54	18	0.41

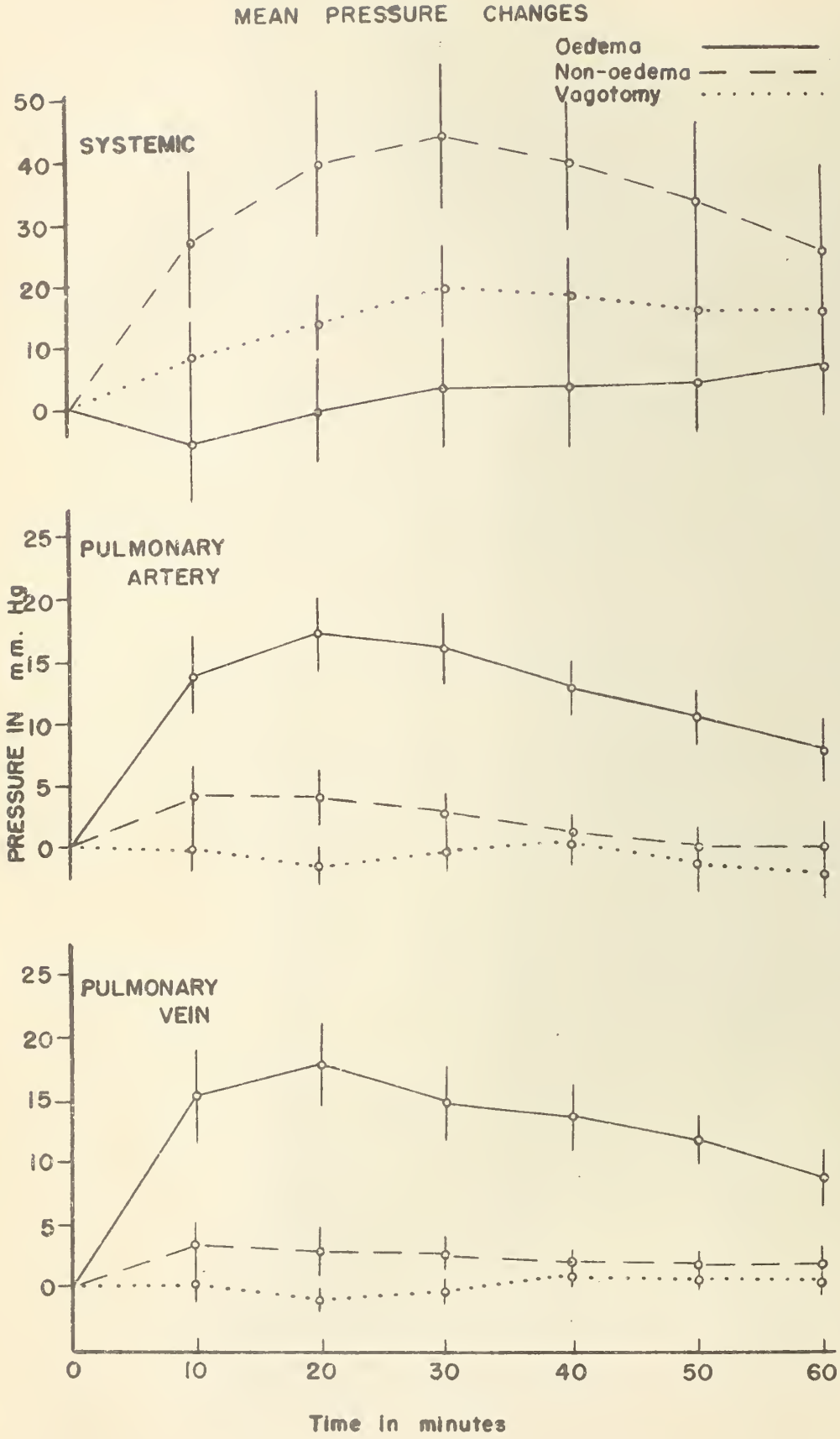

MEAN PRESSURE CHANGES
Oedema
Non-oedema
Vagotomy
SYSTEMIC
PULMONARY ARTERY
PULMONARY VEIN
PRESSURE IN m.m. Hg
Time in minutes
0
10
20
30
40
50
60

Fig. 5

Figure 5.

Mean pressure changes.

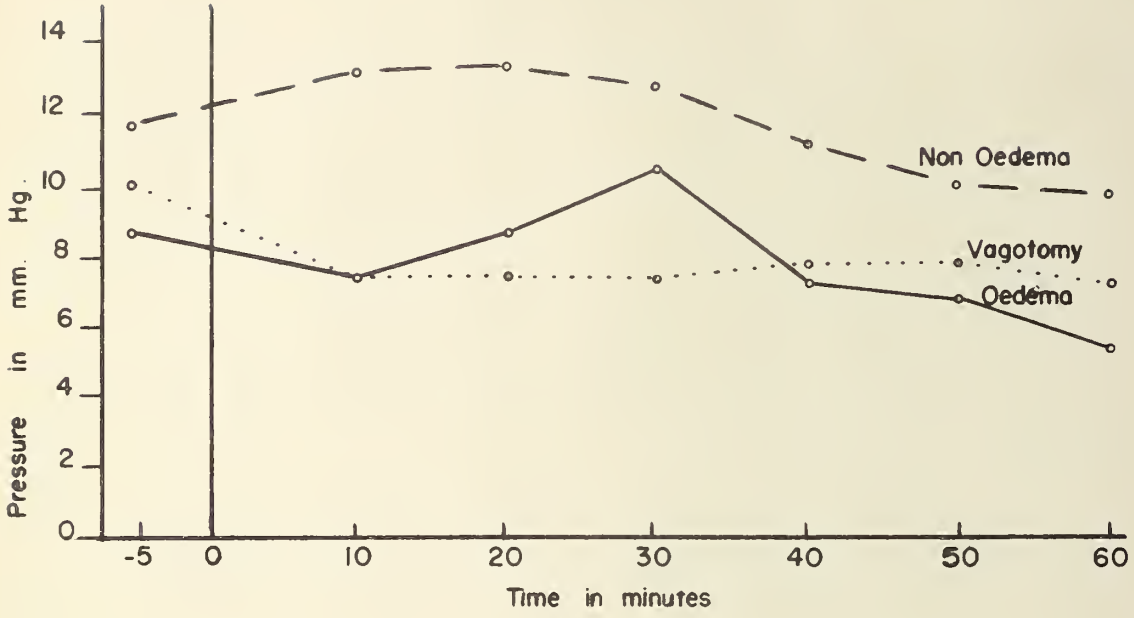
This figure shows the increase in the mean systemic arterial, pulmonary arterial and venous pressures from the pressures in the control period which immediately preceded hypercapnia and vagotomy. There is no significant change in systemic pressure in oedema dogs and a marked increase in non-oedema dogs.

The pulmonary artery and vein pressures are greatly increased in oedema dogs, slightly increased in non-oedema dogs.

The data for dogs with both vagi cut but not breathing CO_2 have also been plotted on the graph. Systemic pressure showed a moderate increase in these dogs while pulmonary pressures are unchanged.

CO_2 data were not plotted in this figure because the resulting graph appeared too confusing. These CO_2 data may be seen in Fig. 4.

PULMONARY ARTERIO - VENOUS
PRESSURE DIFFERENCES



TIME	-5	10	20	30	
S.E.	0·79	1·53	1·15	2·03	← Oedema
	1·98	2·52	2·16	2·08	← Non-Oedema
t	1·43	1·62	2·09	0·94	
P	0·17	0·13	0·06	0·38	

Figure 6.

Pulmonary arterio-venous pressure differences are shown for the data in Fig. 4. The gradient may be seen to be similar in the oedema dogs and in those with vagotomy only.

Statistical data, including standard error of the means, "t" values and probability of random difference are also shown for a comparison of the oedema and non-oedema data.

Only at the 20 minute mark does the difference between these groups yield a "P" value approaching statistical significance.

Table 4a. Comparison of Vascular Pressures in Oedema and Non-Oedema Dogs.

	Time in minutes from control						
	C	10	20	30	40	50	60
Systemic Arterial Pressure							
P $\bar{c}$	155.9	150.6	149.6	159.9	148.8	155.0	159.8
$\bar{s}$	123.6	151.3	162.6	167.6	163.1	156.9	148.0
ΔP $\bar{c}$		-5.3	00.0	3.2	4.0	4.3	7.0
$\bar{s}$		27.8	38.9	43.9	39.2	33.2	25.3
SEx $\bar{c}$		9.7	8.8	8.6	9.6	9.7	9.1
$\bar{s}$		11.5	11.3	11.3	12.4	13.0	14.5
Prob.		0.152	0.014	0.010	0.039	0.090	0.338
Pulmonary Arterial Pressure							
P $\bar{c}$	13.5	27.0	30.5	29.2	25.3	23.1	19.9
$\bar{s}$	13.7	20.2	20.2	18.7	17.2	16.0	16.2
ΔP $\bar{c}$		14.0	17.4	16.4	12.6	10.5	7.3
$\bar{s}$		4.6	4.5	3.1	1.5	0.3	0.5
SEx $\bar{c}$		2.9	3.3	2.8	2.3	2.1	2.6
$\bar{s}$		2.5	2.5	2.0	1.8	1.7	1.8
Prob.		0.026	0.007	0.002	0.002	0.002	0.040
Pulmonary Vein Pressure							
P $\bar{c}$	10.2	20.9	23.2	20.1	18.5	17.8	14.8
$\bar{s}$	4.6	7.8	7.0	.3	6.8	6.8	7.1
ΔP $\bar{c}$		16.0	18.3	15.2	13.8	12.4	9.5
$\bar{s}$		3.2	2.9	2.8	2.3	2.2	2.4
SEx $\bar{c}$		3.6	3.4	2.9	2.6	1.9	2.2
$\bar{s}$		2.5	2.0	1.3	1.0	1.6	1.5
Prob.		0.011	0.001	0.002	0.002	0.001	0.018

P is the pressure in mm. Hg
ΔP is the increase in pressure from the control value
SEx is the standard error of the mean
Prob. is the probability, calculated using the Fisher t test
$\bar{c}$ the dogs with oedema (10)
$\bar{s}$ the dogs without oedema (9)
All of these dogs breathed 30% CO_2 and had bilateral vagotomy.

Table 4b. Comparison of Vascular Pressures in Dogs with Oedema and Dogs having only Vagotomy.

	Time in minutes from control						
	C	10	20	30	40	50	60
Systemic Arterial Pressure							
P $\bar{c}$	155.9	150.6	149.6	159.9	148.8	155.0	159.8
vag.	134.0	142.0	147.0	153.0	150.0	146.0	145.0
ΔP $\bar{c}$		-5.6	0.0	3.2	4.0	4.3	7.0
vag.		8.8	13.3	19.7	18.7	15.8	15.2
SEx $\bar{c}$		9.7	8.8	8.6	9.6	9.7	9.4
vag.		5.5	4.3	6.6	5.1	5.5	5.7
Prob.		0.254	0.262	0.203	0.263	0.356	0.447
Pulmonary Arterial Pressure							
P $\bar{c}$	13.5	27.0	30.5	29.2	25.3	23.1	19.9
vag.	15.5	14.7	13.7	14.5	14.9	13.8	12.4
ΔP $\bar{c}$		14.0	17.4	16.0	12.6	10.5	7.3
vag.		0.4	-1.3	-0.1	0.3	-1.2	-2.2
SEx $\bar{c}$		2.9	3.3	2.8	2.3	2.1	2.6
vag.		2.0	1.8	1.5	1.6	2.4	2.4
Prob.		0.008	0.002	0.002	0.004	0.005	0.047
Pulmonary Vein Pressure							
P $\bar{c}$	10.2	20.9	23.2	20.1	18.5	17.8	14.8
vag.	8.1	9.0	6.2	7.9	9.1	9.1	9.0
ΔP $\bar{c}$		16.0	18.3	15.2	13.8	12.4	9.5
vag.		0.9	-0.7	-0.2	0.6	0.6	0.6
SEx $\bar{c}$		3.4	3.3	2.8	2.6	1.9	2.2
vag.		1.7	1.0	1.4	0.9	1.0	1.4
Prob.		0.008	0.002	0.002	0.002	0.001	0.006

P is the pressure in mm. Hg
ΔP is the increase in pressure from the control value
SEx is the standard error of the mean
Prob. is the probability, calculated using the Fisher t test
$\bar{c}$ the dogs with oedema (10)
vag. the dogs having vagotomy only (7)

Table 4c. Comparison of Vascular Pressures in Dogs without Oedema and Dogs having Vagotomy only.

	Time in minutes from control						
	C	10	20	30	40	50	60
Systemic Arterial Pressure							
P $\bar{s}$	123.6	151.3	162.6	167.6	163.1	156.9	148.0
vag.	134.0	142.0	147.0	153.0	150.0	146.0	145.0
ΔP $\bar{s}$		27.8	38.9	43.9	39.2	33.2	25.3
vag.		8.8	13.3	19.7	18.7	15.8	15.2
SEx $\bar{s}$		11.5	11.3	11.3	12.4	13.0	14.5
vag.		5.5	4.3	6.6	5.1	5.5	5.7
Prob.		0.001	0.001	0.001	0.001	0.007	0.107
Pulmonary Arterial Pressure							
P $\bar{s}$	13.7	27.0	30.5	29.2	25.3	23.1	19.9
vag.	15.5	14.7	13.7	14.5	14.9	13.8	12.4
ΔP $\bar{s}$		4.6	4.5	3.1	1.5	0.3	0.5
vag.		0.4	-1.3	-0.1	0.3	-1.2	-2.2
SEx $\bar{s}$		2.5	2.5	2.0	1.8	1.7	1.8
vag.		2.0	1.8	1.5	1.6	2.4	2.4
Prob.		0.265	0.134	0.297			0.547
Pulmonary Vein Pressure							
P $\bar{s}$	4.6	7.8	7.0	7.3	6.8	6.8	7.1
vag.	8.1	9.0	6.2	7.9	9.1	9.1	9.0
ΔP $\bar{s}$		3.2	2.9	2.8	2.3	2.2	2.4
vag.		0.9	-0.7	-0.2	0.6	0.6	0.6
SEx $\bar{s}$		2.5	2.0	1.3	1.0	1.6	1.5
vag.		1.7	1.0	1.4	0.9	1.0	1.4
Prob.		0.508	0.511	0.148	0.316	0.478	0.405

P is the pressure in mm. Hg
ΔP is the increase in pressure from the control value
SEx is the standard error of the mean
Prob. is the probability calculated using the Fisher t test
$\bar{s}$ the dogs breathing CO_2 and having bilateral vagotomy but not developing oedema (9)
vag. the dogs having vagotomy only (7)

Table 5a. Cardiac Output and Central Blood Volume in Dogs with Pulmonary Oedema.

Date	Wt. (Kgm.)	Time min.	C. O. (l/min.)	C.I. (C.O./m^2)	C. B. V. l	C. B. V. l/Kgm.
Pulmonary Oedema						
20 Sept.	14.4	-30	2.63	6.04	0.64	.044
		-06	2.31	5.31	0.56	.038
		+15	1.125	2.58	0.658	.046
		+55	0.98	2.25	0.577	.040
2 Oct.	11.5	-82	1.68	5.185	-	-
		-75	1.62	5.00	0.32	.028
		+15	1.86	5.74	0.79	.069
		+47	1.38	4.25	0.65	.056
		+121	1.25	3.85	0.76	.066
14 Feb.	11.2	-29	2.12	6.77	0.445	.040
		-08	2.02	6.45	0.455	.040
		+12	0.93	2.97	0.42	.038
		+26	0.73	2.33	0.35	.031
26 March	11.5	-27	1.59	4.90	0.25	.022
		-10	3.15	9.72	0.48	.042
		+13	1.68	5.18	0.37	.032
		+55	1.41	4.36	0.36	.031
		+66	1.53	4.73	0.35	.030
12 March	15	-21	2.39	5.16	0.64	.043
		- 7	2.79	6.02	0.661	.044
		+10	2.21	4.77	-	-
		+40	2.09	4.51	0.654	.044
		+100	1.75	3.77	0.688	.046
19 Feb*	8.0	-22	1.94	9.60	0.34	.043
		-04	0.51	2.52	0.112	.014
		+26	0.70	3.46	0.152	.019

*This data (19 Feb.) is from the dog in which the dye was injected into the pulmonary vein and sampled in the aorta. The volume "CBV" represents the volume of the left atrium and ventricle, a small portion of the pulmonary vein, and the aorta to the tip of the sampling catheter approximately the level of the diaphragm. The best estimate is about 0.131. This is the non-pulmonary portion of the central blood volume in an 8 Kgm. dog.

Table 5b. Cardiac Output and Central Blood Volume

Date	Wt. (Kgm.)	Time min.	C. O. (l/min.)	C.I. (C.O./m^2)	C. B. V. l	C. B. V. l/Kgm.
CO_2 and Vagotomy without Oedema						
12 Feb.	11	-61	1.74	5.70	0.36	.038
		-39	2.99	9.81	0.62	.056
		-06	1.52	5.00	0.34	.031
		+10	1.46	4.78	0.36	.033
		+41	1.37	4.49	0.35	.032
		+72	1.8	5.90	0.43	.039
		+94	1.005	3.29	0.26	.024
21 Feb.	10.5	-46	2.16	7.52	0.45	.043
		-32	2.03	7.09	0.46	.044
		-11	1.56	5.43	0.37	.035
		+ 8	1.17	4.07	0.33	.031
		+29	1.27	4.42	0.35	.033
14 March	9.0	-31	3.17	13.54	0.39	.043
		-10	1.88	8.03	0.30	.033
		+ 7	1.76	7.52	0.33	.037
		+48	0.81	3.46	0.19	.021
28 Feb.	10.8	-31	2.93	9.82	0.67	.062
		- 7	2.93	9.82	0.60	.056
		+ 5	1.81	6.05	0.42	.039
		+27	1.77	5.91	0.44	.041
4 March	9.0	-24	1.26	5.38	0.27	.030
		- 9	1.67	7.13	0.34	.038
		+ 8	1.24	5.29	0.28	.031
		+30	1.31	5.59	0.34	.038

Table 5c. Cardiac Output and Central Blood Volume

Date	Wt. (Kgm.)	Time min.	C.O. (l/min.)	C.I. (C.O./m^2)	C. B. V. l	C. B. V. l/Kgm.
Vagotomy						
25 Sept.	17	-35	1.96	3.58	0.48	.028
		-06	1.28	2.35	0.30	.018
		+17	2.75	5.02	0.76	.045
		+87	1.46	2.68	0.44	.026
		+118	1.58	2.88	0.54	.032
4 Oct.	17	-37	3.79	6.92	0.50	.029
		-15	5.46	9.98	0.78	.046
		-06	4.61	8.42	0.66	.039
		+09	2.92	5.33	0.48	.028
		+59	2.14	3.91	0.41	.024
		+125	1.26	2.30	0.31	.018
9 Oct.	13	-40	1.72	4.49	0.41	.032
		+08	1.19	3.10	0.38	.029
13 Sept.	14.2	-31	1.86	4.40	0.41	.029
		-09	1.48	3.50	0.30	.021
		+05	1.58	3.74	0.38	.027
		+35	1.63	3.86	0.46	.032
		+60	1.97	4.66	0.48	.034
		+86	1.62	3.83	0.42	.029
CO_2 only						
27 Sept.	12.5	-34	1.59	4.39	0.35	.028
		-10	1.93	5.33	0.42	.034
		+ 8	1.62	4.47	0.35	.020
		+36	1.16	3.20	0.26	.021
		+41	0.65	1.79	0.20	.016
		+129	0.67	1.85	0.20	.016
		+150	0.46	1.27	0.12	.007

Blood Flows

Cardiac outputs are shown in Table 5a, 5b and 5c and Figs. 7a, 7b, 7c and 7d. These data were considered too few and scattered to be compared statistically. Each group shows a progressive decline in output, with no apparent differences between oedema, non-oedema and vagotomy. Fig. 7d shows Heath's (1956) data for pentothal anaesthetized dogs breathing 30% CO_2 in O_2. A transient rise followed by a progressive decline in output may be seen.

Central Blood Volume

Central blood volumes, calculated on the basis of litres per kilogram of body weight, are shown in Table 5 and Fig. 8. They appear to be maintained almost constant in the oedema dogs, while there is a gradual decline in the non-oedema dogs, and vagotomy dogs. As in blood flow measurements, statistical comparisons have not been made.

Rabbit Experiments

Results obtained in a pilot series of rabbit experiments are shown in Table 6 below.

Table 6. Rabbit pulmonary oedema experiments.

Date	Weight (kgm.)	Wet/Dry Ratio	Gross Evidence of Oedema	Miscellaneous
CO_2 and both Vagi Cut				
5 Oct.	2.61	6.31	Yes	
17 Oct.	1.65	7.4	Yes	
27 Oct.	3.30	6.56	Yes	
28 Nov.	2.65	7.33	Yes	0.3 ml. Dibenamine
CO_2, Vagi Intact				
26 Sept.	2.54	5.13	No	
28 Sept.	2.57	6.13	Yes	Unusual B.P. results
3 Oct.	3.04	5.13	Very slight	
Both Vagi Cut, no CO_2				
19 Oct.	1.8	5.31	No	
24 Oct.	1.86	5.54	No	
Both Vagi Cut and Sympatholytic Drug				
23 Nov.	3.15	4.91	No	Priscoline
30 Nov.	3.2	5.53	No	Dibenamine
27 Feb.	2.55	5.75	Slight	Dibenamine

In this small series, four rabbits received 30% CO_2 and had both vagi cut, three were hypercapnic only, two were vagotomized only, and three were hypercapnic and vagotomized and also received a sympatholytic drug.

Of the hypercapnic vagotomized rabbits, all four developed pulmonary oedema. One rabbit with intact vagi which breathed CO_2 received very high concentrations for a short while, and stopped breathing. The flows were readjusted to 30% CO_2 while artificial respiration was given and then spontaneous respiration recommenced. When the rabbit was returned to breathing room air, the anticipated post-hypercapnic hypertension did not develop, and at post-mortem, there was gross pulmonary oedema. Although this animal is included in the table it is believed that because of its unusual blood pressure responses it is not representative of the group.

Neither of the rabbits which had been vagotomized only showed pulmonary oedema.

None of the three animals which received a sympatholytic drug, Priscoline or Dibenamine, developed gross pulmonary oedema.

In all of these animals, the wet/dry ratio of the lungs was taken as a measure of pulmonary oedema. All lungs estimated as grossly oedematous on post mortem inspection, had a wet/dry ratio greater than 6.1 : 1, while the non-oedematous ratio was less than 5.6 : 1. One rabbit with a wet/dry weight ratio of 5.75 : 1 was thought to show slight evidence of oedema when the lungs were examined grossly at necropsy.

CARDIAC INDEX WITH OEDEMA

(Co_2 & VAGOTOMY)

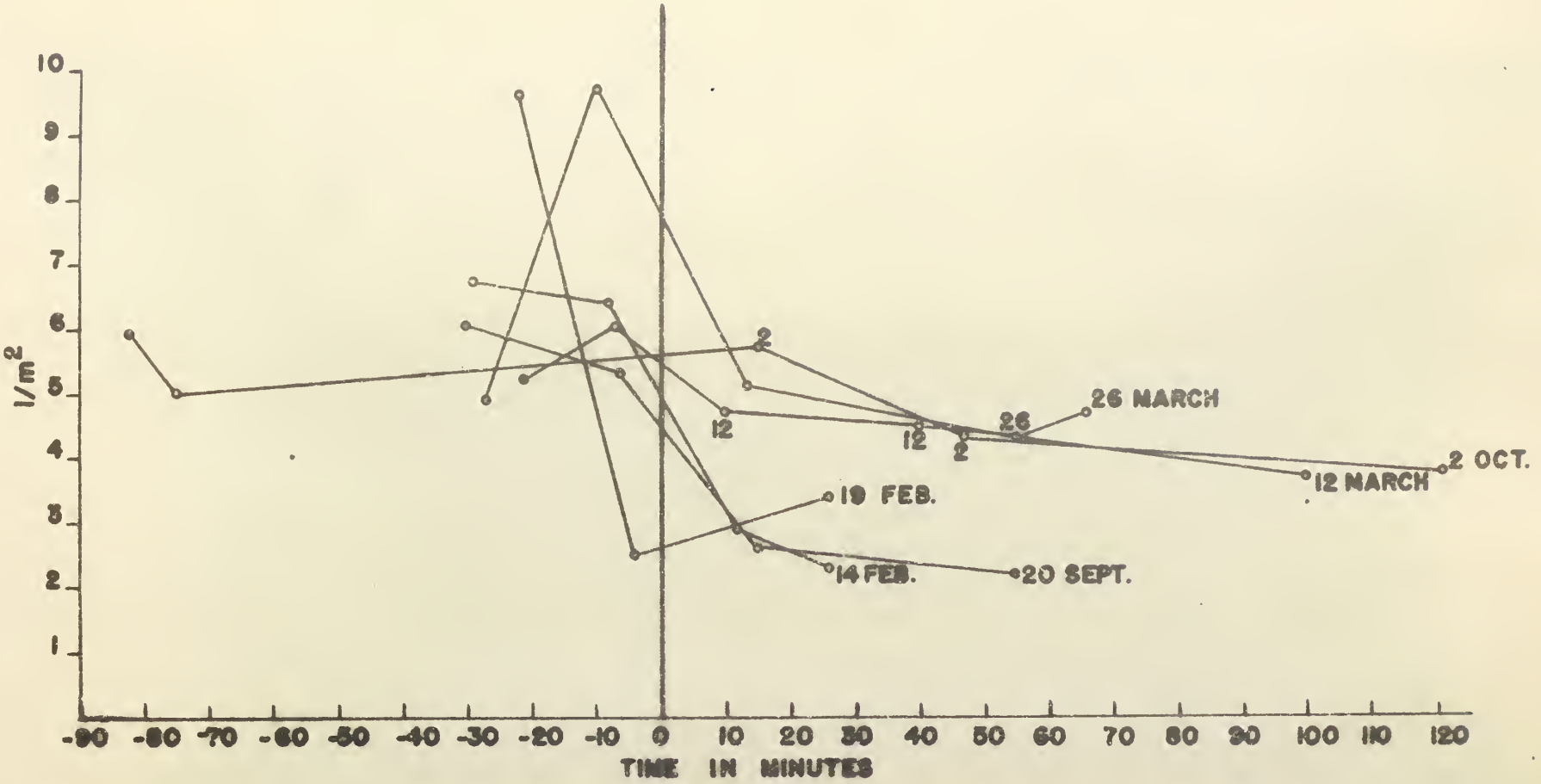


Fig. 7a

Figure 7a.

Cardiac index with oedema.

This depicts the cardiac index, in terms of litres per minute per square meter of surface area, for six dogs which developed oedema. The dogs were started on 30% CO_2, then when pressures had stabilized, the vagi were cut. Time of vagotomy (0 on the time scale) was taken as zero time for development of oedema, hence all curves were brought into register at the time of vagotomy. By inspection, it would appear that output is well sustained for up to two hours.

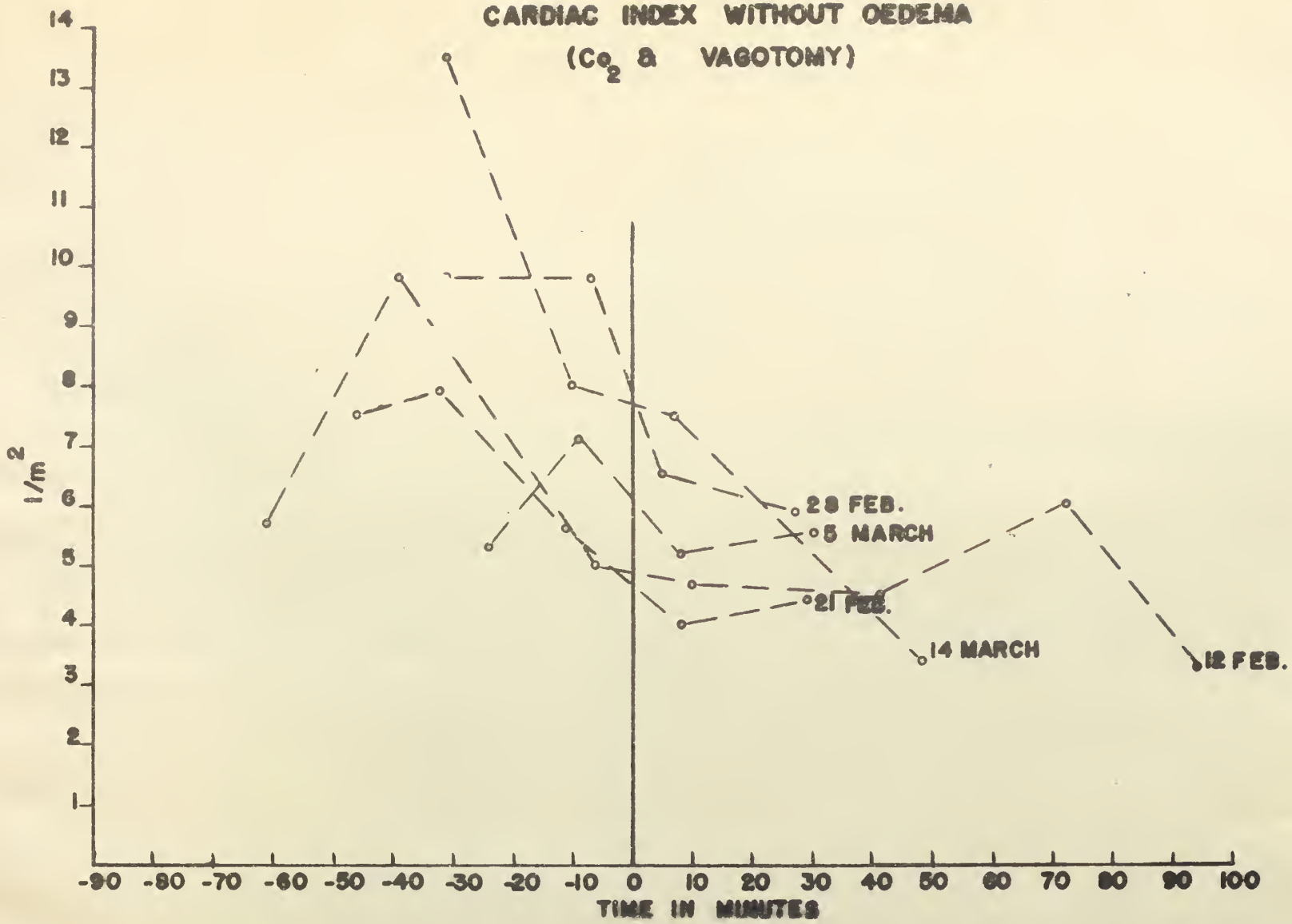

CARDIAC INDEX WITHOUT OEDEMA
(Co_2 & VAGOTOMY)
l/m²
14
13
12
11
10
9
8
7
6
5
4
3
2
1
28 FEB.
5 MARCH
21 FEB.
14 MARCH
12 FEB.
-90 -80 -70 -60 -50 -40 -30 -20 -10 0 10 20 30 40 50 60 70 80 90 100
TIME IN MINUTES

Fig. 7 b

Figure 7b.

Cardiac index, without oedema.

The cardiac indices of five dogs which had CO_2 and vagotomy, but did not develop oedema are shown here. As in Fig. 7a, the same convention of using vagotomy as time "0" is used here. There appears to be a progressive decline in output, more marked than in the oedema group.

CARDIAC INDEX WITH VAGOTOMY

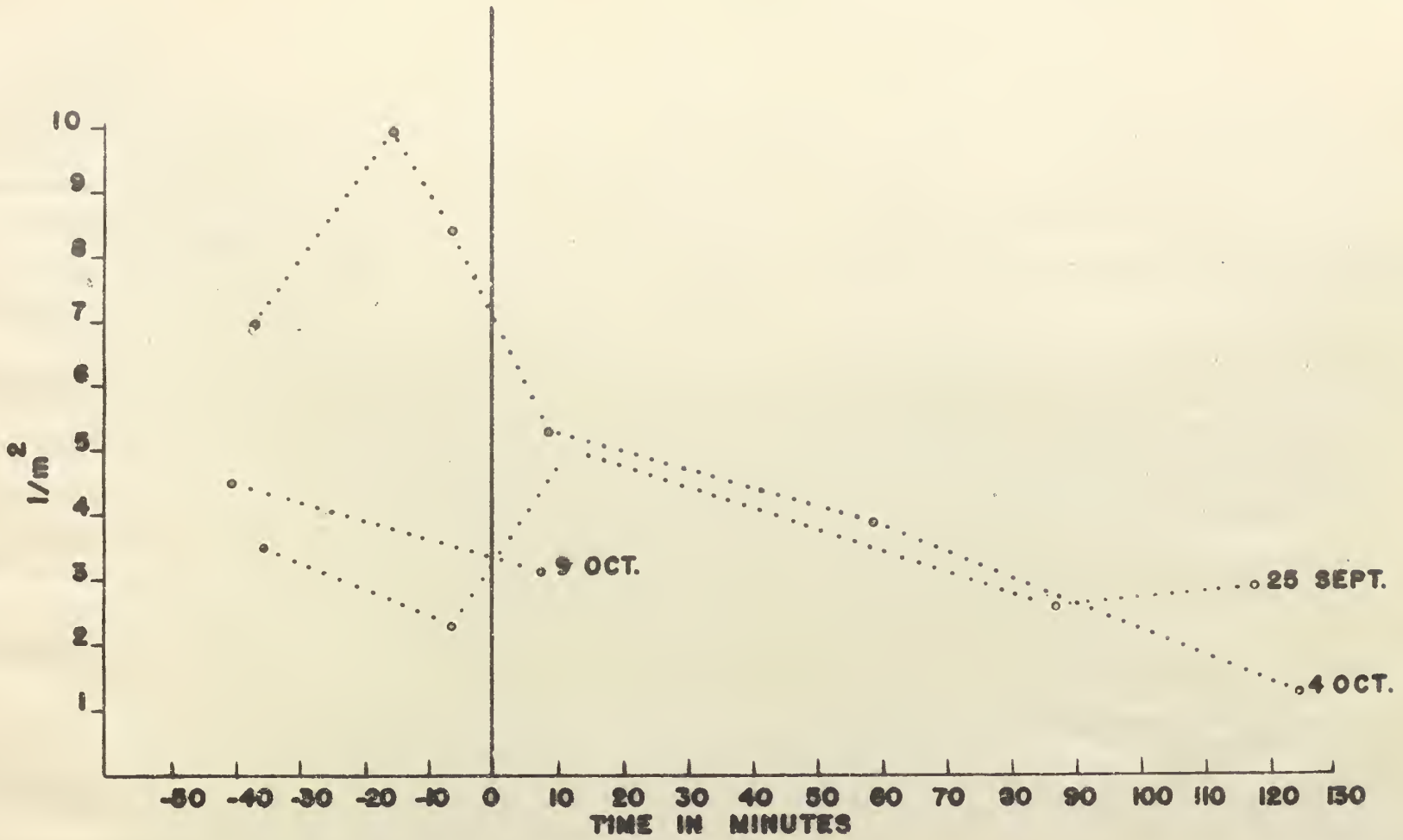


Fig. 7c

Figure 7c.

Cardiac index with vagotomy.

The cardiac indices of three dogs, which had vagotomy only, are shown in this figure. The time of vagotomy is taken as time "0". There is a trend toward a gradual decline.

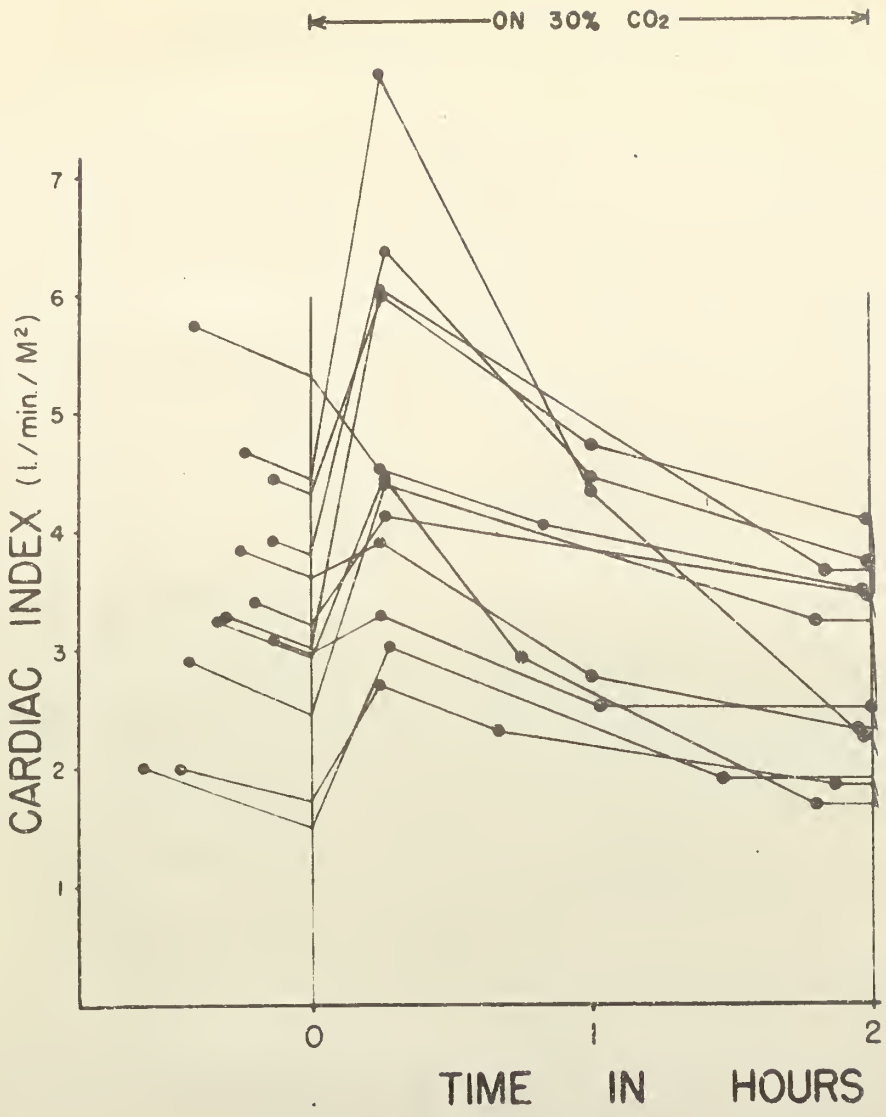


Fig. 7d

Figure 7d.

Cardiac index in hypercapnic dogs.

This figure is taken from Heath (1956) and shows his results in 12 dogs, before and during two hours of hypercapnia. The trend toward decline under thiopentone anaesthesia alone, which may be seen prior to CO_2 administration, had previously been determined and was projected to the zero line. Following the administration of 30% CO_2 there was an increase in output, followed by a decline during the remainder of the time the dogs were hypercapnic.

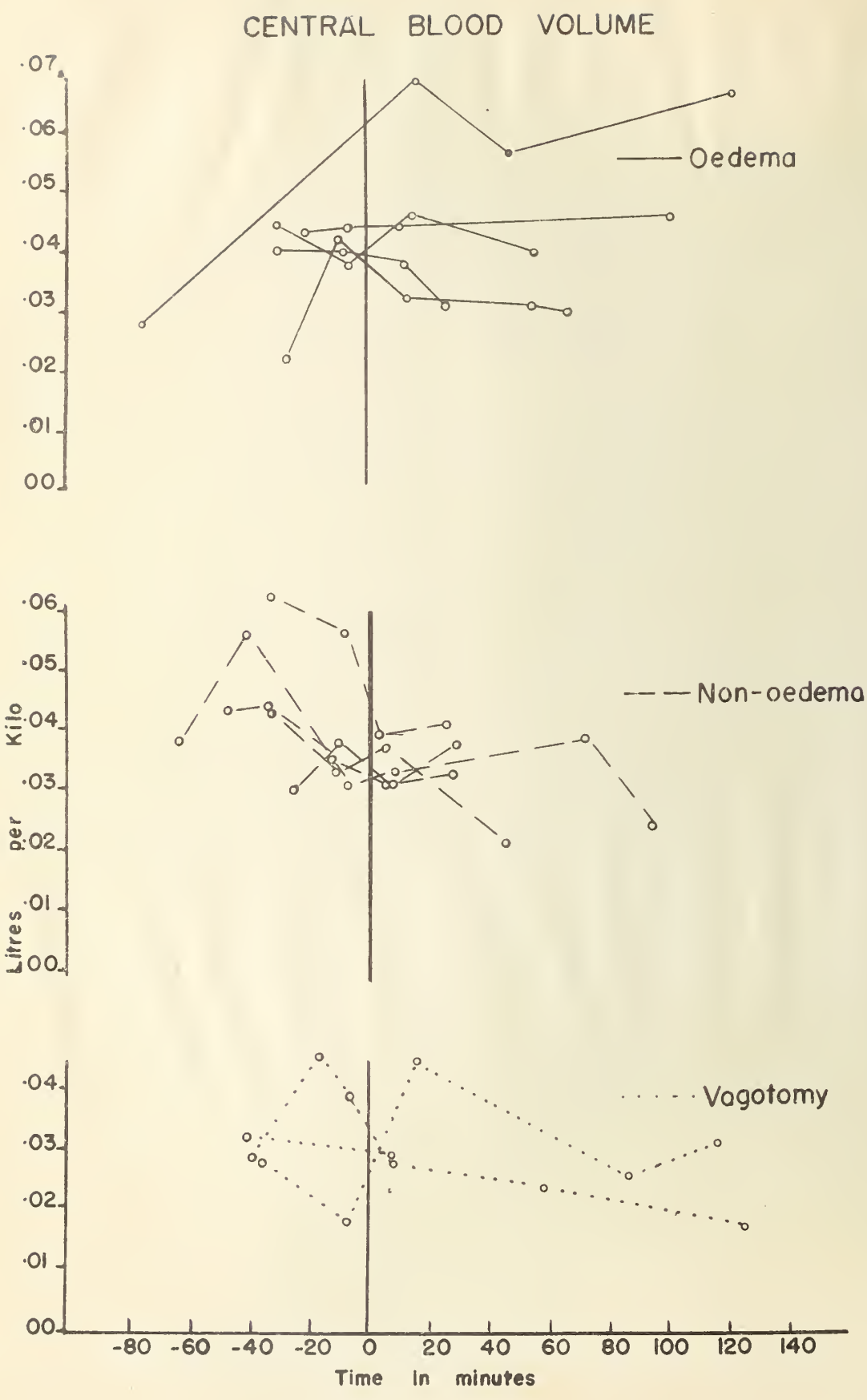

CENTRAL BLOOD VOLUME
·07
·06
·05
·04
·03
·02
·01
00
Oedema
·06
·05
·04
·03
·02
·01
00
Litres per Kilo
Non-oedema
·04
·03
·02
·01
00
Vagotomy
-80 -60 -40 -20 0 20 40 60 80 100 120 140
Time in minutes

Fig. 8

Figure 8.

Central blood volumes estimated from dye dilution curves are shown for three groups of dogs. Vagotomy occurred at 0 time on each graph. Data are widely scattered although values in the oedema dogs appear to be maintained at a higher level after vagotomy than in the other two groups.

Effects of CO_2

It has been shown that 30% CO_2 is well tolerated by intact dogs (Brown and Miller, 1952; Billings and Brown, 1955; Heath, 1956) but not by adrenalectomized dogs (Brown and Miller, Heath, op. cit.). When CO_2 was given to their adrenalectomized dogs, there was the usual immediate fall in blood pressure but the pressure remained at a low level.

Cavert, Johnson and Brown are reported by Brown and Miller (vide supra) to have found that isolated perfused hearts tolerated high CO_2 only if adrenalin was added to the perfusate.

Thirty percent CO_2 has been shown to act as a strong stimulant to the adrenal medulla (Tenney, 1956) and to cause splenic contraction (Billings and Brown, 1955).

In the present series, administration of 30% CO_2 resulted in a rapid increase in the rate and depth of respiration, an immediate drop in blood pressure followed by a rise to just above the control value, and an increase in pulmonary artery and vein pressure. Cardiac output in hypercapnic dogs was found by Heath (1956) to increase to a maximum at 40 to 60 minutes, and then decrease from that time. (See fig. 7d preceding page 39). In the single hypercapnic dog in the present series, in which a number of measurements were made, output was found to decline progressively. (See Table 5c, page 38).

An explanation for these phenomena is proposed. The direct depressant effect of this anaesthetic level of CO_2 (Seevers, 1944) on the cardiovascular system is thought to account for the primary fall in blood pressure seen in all dogs. The stimulant effect of CO_2 on the adrenal medulla and other sites of nor-adrenalin production (Tenney, 1956) results in the release of adrenalin and nor-adrenalin. This is sufficient to restore the cardiac output and peripheral resistance, with a resultant rise in blood pressure. As stated above, this restoration of output has been shown not to occur in the isolated perfused heart nor the adrenalectomized dog.

This response of the sympatho-adrenal system is consistent with the findings of Billings and Brown of splenic contraction following on hypercapnia.

Brickner et al. reported increased mesenteric blood flow during progressive hypercapnia. They reported that resistance, calculated from the pressure drop and the mesenteric blood flow, increased up to CO_2 levels of 4-8% and then decreased up to 16% CO_2. Mean arterial blood pressure increased in the 0-4% CO_2 range, and then progressively declined as the CO_2 level rose. However, it is noted that they used sodium pentobarbital anaesthesia, and it has been reported by Heath (1956) that depression of the cardiovascular system was much more severe in hypercapnic dogs anaesthetized with pentobarbital than in dogs anaesthetized with sodium thiopentone. Therefore it is not considered that their results conflict with the validity of the hypothesis outlined above.

Vagotomy

The vagus nerve has been shown to carry bronchomotor and pulmonary vasomotor fibres (Daly, et al., 1942a, 1942b). It is also well known that the vagus carries afferent impulses of various reflexes (Hoff, 1955). Section of the vagi would be expected to result in the loss of bronchomotor control, minor loss of pulmonary vasomotor control, and some reflexes concerned with regulation of blood volume and heart rate.

There is also deafferentation of some proprioceptors in the thorax, with a resultant increase in thoracic volume in the rest position (Van Liew, 1954). The Hering-Breuer reflex is lost, which would be expected to result in an increased fraction of the respiratory cycle being spent in inspiration, with a decreased mean intra-thoracic pressure.

In experiments reported in this thesis, vagotomy in dogs breathing air resulted in the mean respiratory rate declining to 0.41 of the pre-vagotomy value. See Table 3, page 32. Loss of the vagal inhibitory influence on the heart was qualitatively observed to result in a tachycardia and a slight increase in systemic artery pressure. Pulmonary artery and vein pressures were not significantly affected. See Figs. 4 and 5 preceding pages 31 and 33.

Loss of the reflexes mediated by the vagus was shown by Sarnoff and Sarnoff (1952) to decrease the ability of dogs to tolerate infusions of saline. This would appear to be comparable to the decreased tolerance of vagotomized hypercapnic dogs in this series

to the stress produced by the hypercapnia. Following vagotomy, the hypercapnic dogs showed an increased pulmonary artery and vein pressure, while the air-breathing dogs showed no change in pulmonary vascular pressures.

In all hypercapnic dogs, vagotomy resulted in an increase in mean pulmonary pressures. In the dogs which developed oedema, there was a pronounced increase in pulmonary artery and vein pressures, and therefore an increase in pulmonary capillary pressure, e.g., at 20 minutes following vagotomy, the mean pulmonary vein pressure was 23 mm. Hg. See Table 4, page 36 et. seq., and Fig. 4 facing page 31.

Campbell et al. (1949) found that pulmonary oedema developed in dogs only when pulmonary vein pressure exceeded 20 mm. Hg.

Pappenheimer, Landis and others (quoted by Visscher, 1956) have shown that the pulmonary capillaries are permeable to protein. In the present series of experiments, fluid stained with Evans blue dye, which is known to be protein bound, was recovered from the airways. Increased vascular pressure and hence vascular distention would be expected to increase capillary permeability to protein. This would lower the 'effective' colloid osmotic pressure and hence the pressure at which pulmonary oedema could occur.

Loss of gastro-intestinal motor innervation was not thought to be a factor of consequence in oedemagenesis in the present experiments. All animals had a tracheotomy, which prevented any possibility of aspiration of foreign material.

Cardiac Output

Cardiac outputs in dogs developing oedema do not appear to be different from those in control dogs. Examination of the data from individual experiments gives the impression that in the oedema dogs, outputs do not drop as rapidly as in dogs breathing CO_2 only. It is probable therefore that in oedema dogs cardiac output is at least as high as in non-oedema dogs breathing CO_2 only.

Pulmonary Blood Volume

The central blood volume data shown in Fig. 8 are too widely scattered to establish conclusively what change, if any, has occurred. It does appear, however, that in pulmonary oedema the central blood volume is higher than in the non-oedema dogs. Using this as an index of the pulmonary blood volume, it would indicate that the pulmonary vessels are more distended in dogs which develop oedema than in dogs which do not. Distention of the pulmonary capillaries results in an increased filtration area which in itself would contribute to pulmonary oedema formation.

Dye curves recorded as pulmonary oedema was developing showed a delayed appearance time and prolonged down-slopes (see curves 3 and 4, Fig. 3, preceding page 23, which are typical). Such curves are seen in heart failure or could be caused by an increased dye dilution volume (i.e., pulmonary blood volume) or a combination of both. (In these experiments it would appear that the decreased cardiac output is the major factor causing the curves to be prolonged.)

If we postulate a shift of blood from the peripheral into the pulmonary circuit, such a shift may result from the peripheral vasoconstriction associated with the sympatho-adrenal response to the CO_2 stress. This proportionately greater volume is apparently not enough in itself to cause pulmonary oedema. Heath (personal communication) observed pulmonary oedema only once in over 50 dogs breathing 30% CO_2 in O_2. Loss of the vagal controls results in a further disturbance of pulmonary haemodynamics, with greatly increased pulmonary vascular pressures, and probable greater pulmonary blood volume in some animals.

Effect of Variation in Dogs on Results

The above theory raises the question of why only 13 of 22 hypercapnic vagotomized dogs developed oedema. It would appear that there were some dogs in this group which had a lower systemic arterial pressure prior to hypercapnia, compared to the other dogs. This group of nine dogs showed a sharp rise in systemic pressure following both procedures, while the other 13 dogs showed no significant change. These same nine dogs showed a barely significant rise in pulmonary artery and vein pressures, while the 13 dogs in which the systemic pressure did not change, developed greatly increased pulmonary vascular pressures. This would indicate that some difference in the dogs, the nature of which may only be guessed at, in our present state of knowledge. It is possible that the state of nutrition and adrenal function is the unknown. There is no record of the source of each dog,

but it was noted that they varied from lean scarred semi-wild dogs to fat spayed lap dogs with cataracts. There was no apparent relationship to body weight, season of the year, or gender.

It is here that the findings of Page and Olmstead (1951) and Heath (1956) are of particular interest. Each of these papers mentions the fact that some dogs with higher systemic artery pressures in the control period, responded to the administration of CO_2 in a manner different from the other dogs.

Heath reported that of the five dogs with highest systemic pressure, four showed a decreased systemic pressure when CO_2 was started. The other hypertensive and all 15 normotensive dogs showed the usual increased blood pressure on CO_2 (see Table 1, page 6). While these findings are not directly applicable to this series, it does indicate that the dogs do show individual differences in response.

Immediate Cause of Pulmonary Oedema

Welch's theoryoof pulmonary oedema has been challenged by later investigators (Cameron, 1948). Recently it has been defended by Visscher, Haddy and Stephens (1956) who stress that his theory does not require a prolonged imbalance of output, merely that the imbalance overfill the vascular bed and maintain it in distention. Other factors are not excluded by this theory. They state,

> "Since there is no present evidence that the water movement across the pulmonary capillary walls occurs by any other mechanism than by normal osmotic or hydrostatic pressure gradients, we shall assume that water transport is determined solely by such forces acting across imperfect dialyzing membranes capable of acting as ultrafilters. Therefore we shall assume that lung oedema production is a phenomenon capable of description in terms of movements of water produced by abnormal hydrostatic pressure and concentration gradients across normally or abnormally permeable membranes."

In reviewing the so-called "neurogenic" or "neuropathic" pulmonary oedema, the writer concludes that the neurological lesion is only a remote cause, as in the series of dogs with aortic lesions which was reported by Paine, Smith, Butcher and Howard (1952). These dogs had had part of their aortic valves removed, but were apparently well compensated until they were given adrenalin, or multiple embolization in the brain by carotid injection of barium sulphate. Either of these insults produced cardiac decompensation which caused pulmonary oedema. Similarly pulmonary oedema following increased intracranial pressure was shown by Campbell, Haddy, Adams and Visscher (1949) to be due to the bradycardia and decreased cardiac output, which was accompanied by increased pulmonary vein pressure.

It was also shown by Paine, Howard and Smith (1952) that the incidence of pulmonary oedema in unselected routine autopsies was just as high as in neurological patients.

It has been concluded from the experiments reported herein that the pulmonary oedema developing in some hypercapnic vagotomized dogs can be explained entirely on the basis of the mechanisms outlined by Visscher et al. (1956). High CO_2 is a stressing agent and evokes a

sympatho-adrenal response. This may be comparable to the hypothalamic response described by Gamble and Patton (1951, 1953) and Maire and Patton (1956) following pre-optic and suprachiasmic lesions in guinea pigs. They found that section of the splanchnic nerves gave complete protection from the pulmonary oedema regularly following these lesions, and adrenalectomy gave partial protection. Maire and Patton (ibid.) also showed that there was enough adrenalin in an animal's own adrenals to produce pulmonary oedema if extracted and injected. It had been shown long ago (e.g., Luisada, 1928) that intravenous adrenalin could cause pulmonary oedema, and that this could be prevented by sympatholytic drugs (MacKay, Jordan and MacKay, 1950).

It appears from the four dog experiments and also from the rabbit ones that a sympatholytic agent, e.g., Dibenamine, Regitine or Priscoline, in the recommended dose, can give complete protection from pulmonary oedema caused by vagotomy and 30% CO_2.

Intracardiac Catheters

The effects of passing a catheter through the left side of the heart was felt not to interfere with the function of the heart by Stroud, Stetson and Rahn (1952) who observed no alterations of pulmonary artery pressure as measured via another intracardiac catheter. However, they found that while

dogs survived an indwelling pulmonary artery catheter for extended periods, (up to 56 days without evidence of distress) an indwelling pulmonary vein catheter caused a general deterioration and death in about ten days. At autopsy they found inflammation of the valves, plaques on the vessels, and interlaced antemortem clots about the catheter.

Apart from the one dog which died in acute pulmonary oedema very soon after the catheters were passed, no evidence was seen that the presence of the catheters was a source of embarrassment to the dogs.

Anaesthetic

Sodium thiopentone was used in these experiments because of its short action. CO_2 in 30% concentration is a potent anaesthetic agent, and it was observed by Heath (1956) that this degree of hypercapnia superimposed on pentobarbital anaesthesia led to a severe degree of depression. This depression was not observed in dogs lightly anaesthetized with thiopentone.

In this series, anaesthesia was induced with 25 to 30 mgm. per kilogram of body weight, which permitted the initial procedures to be carried. Small supplementary doses were given as and if required. Dogs breathing CO_2 required no further thiopentone.

Whitehead and Virtue (1954) state that Pentothal acts by "depressing the internuncial spread of pain impulses in the brain, thereby inhibiting the psychic phase of pain experience. These concepts would be in line with studies which have shown that barbiturates act selectively on the internuncial neurons rather than on afferent motor pathways."

Barbiturates are noted for having a depressant action on the respiratory centre, decreasing the rate and depth of breathing, occasionally causing an irregular rhythm. This is in the main a direct depression of the medullary respiratory centre, although the sino-aortic chemoreceptors may also be affected (Gruber, 1937). The respiratory centre becomes progressively less sensitive to CO_2 (Draper and Whitehead, 1949). The injection of thiobarbiturates intravenously in dogs and monkeys was found (Gruber, 1941) to cause a brief rise in blood pressure of up to 50 mm. Hg, accompanied by a decrease in the volume of the spleen and kidney, and usually by cardiac irregularities.

Evidence of the effect of Pentothal on the cardiac output is incomplete. Gresheimer et al. (1953, 1954 and 1956) reported an increased output in dogs; Heath and Brown (1956) reported the highest cardiac output at 40 to 60 minutes after induction, with a progressive decline from that time.

In our experiments an attempt was made to keep the anaesthesia as light as was compatible with unresponsiveness. This was necessarily judged on an empiric basis. In this connection,

Stroud and Rahn (1953) using pentobarbital (Nembutal) reported a similar situation. They found that a standard dose by weight did not give a constant depth of anaesthesia, but that the result was strongly affected by the relative amounts of fat and muscle.

These authors emphasized the important role that might be played by the anaesthetic agent used. They stated that it is recognized that barbiturates are directly depressant to the vasomotor centre and have a direct dilating action on the smaller vessels. They found that in animals deeply anaesthetized with Nembutal (pentobarbital) breathing 5% O_2 caused very little rise in pulmonary artery pressure. When the anaesthesia was allowed to lighten the hypoxia caused a more pronounced rise in pressure, and when the experiments were repeated on conscious dogs 8% O_2 caused a much more pronounced rise in pulmonary artery pressure.

Heparin

Heparin was used as anticoagulant in those dogs in which the cardiac output was measured. The initial dose was 1.5 to 2 ml. of 1:100 solution given intravenously and reinforced as required.

Heparin has been reported to lessen the development of pulmonary oedema by a direct action on the pulmonary capillaries (Luisada and Contro, 1953). In our series heparin did not prevent pulmonary oedema in 13 dogs but may possibly have contributed to the failure of oedema to develop in the others.

Artificial Ventilation

Pulmonary oedema did not develop in any of the dogs which required artificial ventilation. It has been shown by many workers, e.g., Watrous, Davis and Anderson (1950), Bjurstedt and Hesser (1953, Barron (1955), Rushmer (1955) that positive pressure ventilation decreases cardiac output and arterial pressure, and increases central venous pressure. The net effect of removing the usual negative pressure in the thorax, and replacing with positive pressure, is to impede the venous return to the thorax, and facilitate ejection which results in a decreased amount of blood in the lungs. This would tend to decrease the likelihood of pulmonary oedema.

Position

All dogs in this series were positioned supine, which in itself is a disturbance of the animal's haemodynamics. Rahn, Sadoul, Farhi and Shapiro (1955) measured lung blood flows and ventilation in various parts of the lung, with the dogs erect and supine, using radio-active tracer methods. They found that there was increased blood flow and decreased ventilation in the dependent lobes, i.e., increased blood volume. However, this tendency to congestion was constant in all dogs in the present work.

SUMMARY OF RESULTS

Pulmonary oedema developed in 13 of 22 dogs which breathed 30% CO_2 and had a bilateral cervical vagotomy. The systemic artery, pulmonary artery and pulmonary vein pressures were measured in these dogs, in seven dogs which were vagotomized only, in three dogs which were hypercapnic only, and in three dogs which were given both lesions and also sympatholytic drugs.

It was found that the most significant change in pressure was an increase in pulmonary vein pressure, in dogs which later developed pulmonary oedema, following the CO_2, and a further increase after vagotomy. The non-oedema dogs, under the same conditions, showed a lesser increase in pulmonary pressures following CO_2 and no change after vagotomy. Dogs breathing air showed only minor changes in pulmonary vascular pressures following vagotomy.

It has been postulated that there was some selection of dogs, in that the systemic arterial pressure of the oedema dogs was higher during the control period than the systemic pressure of the non-oedema dogs. There was a greater increase in pulmonary artery and vein pressures after CO_2 and again after vagotomy, in the oedema dogs.

The pulmonary oedema which developed in some hypercapnic vagotomized dogs has been explained entirely on the basis of altered haemodynamics, with a shift of blood into the pulmonary circuit, an increase in pulmonary capillary pressure and distention of the pulmonary vascular bed. There is no need to invoke an increase in permeability due to loss of vascular innervation.

It is suggested that the stress of high CO_2 stimulates adrenalin and nor-adrenalin production, tending to mitigate the depressant effects of the hypercapnia. Vagotomy removes the afferent limbs of some regulatory reflexes and also removes the major regulatory mechanism of the heart. This second lesion is sufficient to produce, in some dogs, a further increase in pulmonary vascular pressures comparable to high output failure.

No explanation is offered for the apparent selection of dogs which resulted in only 13 of 22 dogs developing pulmonary oedema. Other workers have found similar discrepancies in response of dogs to hypercapnia.

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